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ADSORPTION OF METHYLENE BLUE BY BLOOD OF INFANTS AND CHILDREN

MECHANISM OF REACTION AND CLINICAL APPLICATION

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In the relation between the red blood cells and their environment, the occurrence of adsorptive phenomena is to be expected. The extensive surface presented by the red blood cells and its intimate contact with the diversity of substances contained in plasma provide opportunities for adsorptive processes comparable to those which occur at other interfaces. There have been relatively few studies in which this property of the red blood cells has been investigated.

In a previous study [1] a phenomenon was described in which dilute solutions of methylene blue (methylthionine chloride) were decolorized by blood under well defined experimental conditions. Many of the features could be accounted for on the basis of adsorption, and the evidence indicated that the red blood cell was the most important element involved in removal of the dye from solution. The decolorization phenomenon was demonstrated as follows: When a sample of blood from a healthy infant was mixed with a dilute solution of methylene blue in sodium citrate and exposed to the cold, the solution was rapidly decolorized. The supernatant layer contained no methylene blue, and when the sediment was washed several times with cold citrate solution, each of the washings returned clear. That the dye had been adsorbed by the red cells was shown when the washed cellular sediment was resuspended in citrate solution and exposed to warmer temperatures. The dye now reappeared in strong concentration in the surrounding medium. It was noted at that time that the blood of the young infant during the first four months of life possesses the unique property of

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1. Smith, C. H.: Reduction of Methylene Blue by the Blood of Young Infants, Am. J. Dis. Child. **49**:1189 (May) 1935.

decolorizing the solution of dye most rapidly, a reaction shared by the young rabbit and guinea pig.

In the course of this study it was observed that the blood of older infants and children could also decolorize methylene blue solutions but more slowly and not to the extent produced by the blood of young infants. It was further noted that illness in some manner interfered with the process of decolorization at any age period. Since the latter observation suggested a clinical application of this reaction, a series of tests was carried out with a simplified procedure which would apply to persons of any age period. The present communication is concerned with the results of these tests as well as with a more extensive analysis of the mechanism of methylene blue adsorption by the red blood cells. In this paper the decolorization of solutions of dye by the red blood cells can be no longer referred to as reduction, the term used in the previous communication. The evidence derived from the present study confirms the opinion expressed in the earlier paper that when the solutions lose their color it is due not to reduction but to adsorption of chemically unaltered dye by the red blood cells.

METHOD

A stock solution of dye was prepared as follows: Three hundred milligrams of methylene blue was dissolved in 100 cc. of a 3 per cent solution of sodium citrate; after standing several hours at room temperature the solution was placed in the ice box. One cubic centimeter of this solution was then dissolved in 100 cc. of a 3 per cent solution of sodium citrate, so that the final concentration of the reagent was 3 parts of the dye in 100,000 parts of the solution. For the test, 0.2 cc. of the latter solution was placed in a tube 1 cm. in width by 8 cm. in height, and to this 0.1 cc of blood obtained by deep puncture of a finger tip was added with a calibrated 0.1 cc. pipet.[2] The dye and the blood were thoroughly admixed, and with a Wright pipet the contents were transferred to a narrow tube 7.5 cm. long, with an inside diameter of 4 mm. The tube was immediately placed in the ice box. Three identical tests were carried out at the same time with three consecutive aspirations of 0.1 cc. of blood. Since the phenomenon depends on adsorption of the dye by red blood cells in the cold and its release at a higher temperature, it is essential that the time interval between the initial mixture of the dye and blood and transfer to the narrow tube and placement in the ice box be as brief as possible, preferably under ten minutes. This precaution is to be observed especially on warm days, when a beaker with ice should be provided for the tubes containing blood and dye.

Usually the red blood cells settled out in a few hours, but the depth of color of methylene blue in the overlying column of plasma was not recorded until at least eighteen hours had elapsed from the time the tubes were placed in the ice box. It is advisable not to extend the period before reading beyond twenty-four hours, since after this time decolorization begins to take place in all specimens at varying rates of speed. The degree of decolorization ranged from 0, when the only change in the color of the dye was caused by its dilution with plasma, to 4 plus, in which case the solution was completely decolorized, so that the supernatant

2. This pipet was the same as that employed in the sedimentation test, which will be referred to later.

liquid possessed a clarity often like that of water, although usually it was faintly tinged with bluish green. For purposes of record, comparison of the supernatant fluid for depth of color was made with varying concentrations of solution of the dye. The supernatant fluid from at least two of the tubes was combined; it was transferred to one of the narrow tubes with a Wright pipet and was placed in the middle hole of the front row of a comparator, and a tube of water was placed behind it. Tubes containing standard colors were prepared by diluting the solution of methylene blue (3: 100,000) with a 3 per cent solution of sodium citrate. Four dilutions were prepared, 1 part of the dye being mixed with 1, 3, 6 and 12 parts of the solution of sodium citrate in tubes designated as 1, 3, 6 and 12, respectively. Equal quantities of solutions of each of these strengths were pipetted into tubes of the same dimensions as those containing the supernatant fluid (4 mm. by 7.5 cm.). As is customary in matching, tubes with concentrations of the dye approximating that of the sample were placed on either side of it. Since the supernatant fluid contained traces of pigment in addition to the unadsorbed methylene blue, appropriate strengths of potassium bichromate were employed for more accurate comparison. Behind the standards in the comparator, therefore, tubes were placed containing solutions of potassium bichromate of 1 : 2,000, 1 : 5,000 and 1 : 10,000 concentrations, and these corresponded in position to the tube of water behind the sample to be matched. The depth of pigment was usually controlled by the tube containing the 1 : 10,000 dilution of potassium bichromate. The concentrations of methylene blue still present in the supernatant fluid after adsorption of the dye by the red blood cells were noted as follows: 0 indicated the range in depth of color between tubes 1 and 3; 2 plus, that between tubes 3 and 6; 3 plus, that between tubes 6 and 12, and 4 plus, that between 12 and a tube containing water. There was no difficulty in judging 0 (absence of reduction), 3 plus (moderate) or 4 plus (maximum) reduction.

It was soon apparent that during the acute stage of disease the erythrocytes sedimented rapidly, even in the cold, in the tubes containing the mixture of methylene blue and blood, leaving a deep blue supernatant layer. On the contrary, in the case of well children the opposite usually resulted, namely, slower rates of sedimentation with an overlying column which, with few exceptions, was decolorized moderately or markedly. Although cold retards the sedimentation of red blood cells, it was nevertheless obvious that the speed of this reaction was closely associated with the extent to which the solution of dye was decolorized. The sedimentation rate of the red blood cells at room temperature was therefore determined with every methylene blue test in the cold, and the results were compared. The sedimentation rate also constitutes a sensitive index of infection, since it may remain rapid during the terminal stages of disease and during convalescence even when the white cell count has reached a normal level. The volume of packed red blood cells was also determined in every instance, in order that the sedimentation rate might be evaluated more accurately and that the results might serve as an additional aid in judging the progress of the disease in cases of anemia.

When the specimens were collected for the adsorption tests, blood was obtained at the same time for hematocrit and sedimentation tests, and in a large number of instances for complete blood counts as well. Hellige hemometer tubes and standardized pipets were employed for the counts. The sedimentation rate was determined with citrated blood by a finger puncture method[3] which had been

3. Smith, C. H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children with the Use of Capillary Blood, Am. J. M. Sc. **192**:73 (July) 1936.

devised for use with younger age groups. Although readings for the sedimentation rates were made at fifteen minute intervals, it was obvious that for the purposes of this investigation the number of millimeters traversed by the red blood cells in one hour was entirely satisfactory as the sole measure of comparative rates of sedimentation. For the single determination at the end of one hour, the average was 9 mm., with a variation of from 3 to 13 mm. For purposes of classification, 13 mm. in one hour was regarded as the upper limit of normal sedimentation. The volume of packed red blood cells, expressed as the percentage of whole blood, was determined by use of the sedimentation tube as a hematocrit and with heparin as the anticoagulant. Use of the latter permitted the estimation of the volume of packed cells in undiluted and unaltered whole blood. On the basis of data from several sources, the value of 36 per cent for the hematocrit reading was designated as the minimum normal level for the group of older infants and children under consideration in the present study.

RESULTS

The data for analysis comprised 576 observations on 227 infants and children ranging in age from 5 months to 14 years. Since one of the primary purposes of this study was to determine whether the degree of decolorization of methylene blue could be correlated with the activity of a pathologic process, the results for infants in the first four months of life were not included. This restriction was based on the observations in the previous study,[1] which revealed the remarkable decolorizing capacity of the blood of infants of this age period. It was thought that this property might overshadow finer gradations of adsorption of dye during the period of recovery from infection. In the few instances, however, in which the blood of sick infants was studied during the first few months of life, the reactions conformed to those of older persons. It may also be noted that the technic applied in the present study was suitable in demonstrating the increased decolorizing capacity of the blood of the healthy infant under 5 months of age.

The results include several groups of observations. The main group was derived from periodic examinations of the blood of children who had a variety of pathologic disorders, usually of an infectious nature. Samples of blood were taken during the acute stage of illness and during the course of convalescence. Another group consisted of observations on well children, and a third, of those on children with nutritional anemia who were undergoing treatment with iron. The observations of the last group were so uniform in regard to response to adsorption of dye and deviated so markedly from the majority of results in several important respects that they will be considered separately. After the results for the children with anemia were excluded, the remaining 460 observations were summarized with respect to the degree of adsorption of dye, sedimentation rate and volume of packed cells (table 1).

It will be noted that the degree of adsorption was closely correlated with the average sedimentation rate for each group. That the intensity of adsorption was related to the activity of disease was borne out

clinically, as decolorization was absent during the stage of acute illness and was manifest during defervescence and recovery. The volume of packed cells has been regarded as exercising a direct influence on the sedimentation rate, the more rapid rates occurring with lower hematocrit readings. Exceptions to this principle have recently been noted for a group of young children with nutritional anemia,[4] for other age groups and for patients with other conditions.[5] It will be noted in table 1 that the average volume of packed cells for each group varied so little that the rate of sedimentation and the degree of decolorization represented primarily the influence of the pathologic process.

As observed in this table, however, the range of sedimentation rate for all groups showed variation, which indicates that exceptions to the correlation between decolorization and rate of sedimentation occurred. Analysis of the data on which this table was based revealed that the

TABLE 1.—*Summary of Tests on Adsorption of Methylene Blue in Relation to Sedimentation Rates and Hematocrit Values*

Group	Adsorption, Degree of Decolorization*	Sedimentation Rate, Mm. in 1 Hr.		Volume of Packed Red Blood Cells, Cc. per 100 Cc.		No. of Observations	No. of Cases
		Average	Range	Average	Range		
A	None (0)	23.9	9-35	38.5	23-47	146	75
B	Intermediate (2)	16.9	3-32	39.2	26-47	103	71
C	Moderate (3) and marked (4)	11.6	2-32	40.5	32-53	211	134

* In this table and in the accompanying tables, the degrees of decolorization range from 0, in which no change has occurred, to 4 plus, in which decolorization of the solution is complete. The plus designation has been omitted, and the values are noted simply as 0, 1, 2, 3 and 4.

correlation between the two measurements was greater for group A than for group C. Group B will be omitted from the present consideration because intermediate grades of decolorization may have been subject to individual interpretation, whereas the degree of adsorption of dye was more readily measured for the other two groups.

In group A, which comprises observations made during the period of acute illness, there were only 12 instances in which no decolorization occurred but in which the sedimentation rate was normal. In 92 per cent of the observations the blood did not decolorize the solution of methylene blue and the sedimentation rate was rapid (14 mm. or more in one hour). In group C, however, there were 61 instances in which the sedimentation rate was increased but in which moderate degrees of decolorization occurred. The agreement in the two types of tests was approximately 71

4. Smith, C. H.: Sedimentation Rate in Nutritional Anemia of Infants and Children: Its Response to Treatment with Iron (Ferrous Sulfate), Am. J. Dis. Child. **56**:510 (Sept.) 1938.

5. Cutler, J. W.; Park, F. R., and Herr, B. S.: Influence of Anemia on Blood Sedimentation, Am. J. M. Sc. **195**:734 (June) 1938.

per cent. The discrepancies in this group occurred with the blood of children who either had passed the acute phase of their illness and were recovering or were ambulatory with mild infections. In these cases judgment as to the clinical status was often equivocal; the white cell counts were usually within the normal range, and the sedimentation rates were accelerated to a moderate degree only. Thus, of the 61 instances in which discrepancies were shown, the sedimentation rates were from 14 to 16 mm., inclusive, in 30 and from 14 to 18 mm., inclusive, in 43. There were relatively few pronounced discrepancies. One occurred in the case of a child who had rheumatic disease with nodules but did not appear ill clinically. In this case the sedimentation rate varied from 24 to 32 mm., and in 4 tests moderate decolorization took place. On the other hand, in the case of another child who seemed well, whose physical examination revealed only markedly hypertrophied tonsils, the sedimentation rate in 3 tests varied from 9 to 13 mm., but the blood did not decolorize the solution of methylene blue. During this period of observation, the sedimentation rate in 1 test rose to 20 mm., for no explained reason, and in this instance also decolorization was absent.

Included in table 1 are 89 observations on the blood of 64 well children. The intensities of decolorization were distributed as follows: Decolorization was moderate or marked in 81 tests, or 91 per cent; intermediate in 4, and absent in 4. The last 4 tests were made on the blood of the child just mentioned. In 4 children of this group the sedimentation rate was increased, for no accountable reason, but moderate decolorization occurred. For 3 children with no physical abnormality, only intermediate grades of decolorization were noted. The results point, therefore, to the conclusion that decolorization occurs, with few exceptions, in the blood of healthy infants and children and that it disappears during the active stage of disease, to return at a variable period during recovery.

In table 2 are presented typical cases in which the blood failed to remove the dye from solution during the active phase of infection and in which the solution was decolorized when the infection subsided. It will be observed that the volume of packed cells cannot be considered a major determining factor of the capacity of the red blood cells to remove the dye from solution. Within certain limits the quantitative mass of cells was therefore of less importance in its relation to adsorption of methylene blue than was the rate of sedimentation. The fluctuations of the sedimentation rate and the degree of decolorization of the dye, however, usually revealed parallel changes. While the hematocrit reading showed a narrow range of variation, a reaction of 3 plus, or a moderate degree of decolorization, did not usually occur until the sedimentation rate was slowed to about 13 mm. per hour, the upper limit of normal values.

The exceptions to the parallelism between the sedimentation rate and the degree of adsorption of methylene blue which, as pointed out, occurred in a few instances in group A and more frequently in group C, are exemplified in several of the cases in table 2. In the case of S. B., on December 31 an increased sedimentation rate of 15 mm. in one hour was associated with a moderate degree of decolorization, whereas in that of R. A., on November 11 blood with only a slightly accelerated

TABLE 2.—*Examples of Changes in Adsorption of Methylene Blue in Blood of Children with Various Pathologic Conditions*

Case No.	Patient	Age, Yr.	Date	Adsorption, Degree of Decolorization	Sedimentation Rate, Mm. in 1 Hr.	Volume of Packed Red Blood Cells, Cc. per 100 Cc.
1	M. B. (pneumonia)	2½	2/16/37	0	16	46
			2/28/37	2	10	41
			3/ 6/37	2	10	40
			3/16/37	3	5	40
2	I. N. (pneumonia)	3½	4/26/35	0	30	40
			4/30/35	0	30	43
			5/ 2/35	0	24	44
			5/ 7/35	2	15	40
			5/11/35	3	12	42
3	E. T. (pneumonia)	6	10/16/37	0	27	40
			10/16/37*	0	28	40
			10/17/37	2	27	40
			10/19/37	2	24	42
			10/26/37	3	12	42
			10/28/37	3	13	40
			3/12/38	3	12	38
4	D. J. (infectious mononucleosis)	5	8/21/35	0	17	40
			8/25/35	0	17	38
			11/26/35	3	9	38.5
			12/10/35	2	7	38
			12/26/35	3	7	40
			1/16/36	3	6	38
			3/12/36	3	11	38
5	R. A. (rheumatic disease)	6	10/26/34	0	24	37.5
			10/27/34	0	24	39
			11/ 1/34	0	20	42
			11/11/34	0	14	38
			5/ 4/35	3	11	43
			9/28/35	3	13	39
6	S. B. (bronchiectasis)	11	11/ 2/35	0	30	36
			11/19/35	2	21	37
			12/31/35	3	15	41
			3/28/36	3	12	40

* The second examination of the blood on October 16 was made five hours after the first.

sedimentation rate of 14 mm. showed absence of decolorization. It will also be noted that in the cases of children with infection included in this table, absence of decolorization occurred with sedimentation rates which ranged from 14 to 30 mm. in one hour. On the other hand, moderate, or 3 plus, decolorization will be noted for rates ranging from 5 to 15 mm. While these observations confirm the principle that slowly sedimenting red blood cells adsorb more methylene blue than those which settle out more rapidly, the variations within each group suggest, nevertheless, that red blood cells of different specimens possess individual capacities for adsorption of dye.

NUTRITIONAL ANEMIA

There were 116 observations on the blood of 20 infants and children with nutritional anemia who received iron therapy. In another study it had been shown that the sedimentation rate of the blood of 16 of these patients was slower than might be expected with diluted normal blood.[4] It was suggested that the red blood cells of these children underwent qualitative alterations during iron medication at the same time that they increased in number and in hemoglobin content. The observations presented in table 3 lend further support to this hypothesis.

In 5 of the 116 observations of this group the sedimentation rate varied from 17 to 40 mm. before the institution of therapy; the volume of packed cells ranged from 12 to 31 per cent and decolorization was absent. When the 3 observations of the intermediate group in which

TABLE 3.—*Summary of Tests on Adsorption of Methylene Blue in Cases of Nutritional Anemia in Relation to Sedimentation Rates and Hematocrit Values*

Group	Adsorption, Degree of Decolorization	Sedimentation Rate, Mm. in 1 Hr.		Volume of Packed Red Blood Cells, Cc. per 100 Cc.		No. of Observations	No. of Cases
		Average	Range	Average	Range		
A	None (0).....	28.4	17-40	23.4	12-31	5	5
B	Intermediate (2).....	22.3	13-26	30.0	21-36	3	3
C	Moderate (3) and marked (4)						
	Total.....	10.2	2-32	35.9	18-44	108	20
	1. Rapid sedimentation (14 mm. or more).....	19.1	14-32	32.0	18-40	27	10
	2. Normal sedimentation (13 mm. or less).	7.2	2-13	37.3	26-44	81	20

the readings were sometimes equivocal were excluded, the remaining 108 observations were subdivided into two groups with reference to the sedimentation rate: a group with the rapid rate of 14 mm. or more in one hour and one with the normal rate of 13 mm. or less. Whereas normal adsorption would be expected in the latter group alone, on the basis of the results for the nonanemic children, it is noteworthy that the rapid sedimentation rates for the anemic children were accompanied by moderate and marked degrees of adsorption of methylene blue. This began during the early stages of iron therapy, when the sedimentation rate was still rapid and before the hematocrit reading reached a normal level. As previously stated, 36 per cent was designated as the minimum normal volume of packed cells for the infants and young children with nutritional anemia in this series. The decolorization with rapid rates of sedimentation in cases of nutritional anemia may be contrasted with the expected failure of the blood to decolorize the solution of dye in cases of active disease, as already noted.

The marked decolorizing capacity of the blood of subjects with nutritional anemia after adequate iron therapy is further suggested by a comparison of the number of observations for anemic children in which a 4 plus reaction was obtained with the number for the non-anemic group. This degree of decolorization represents the most active removal of dye by the blood and corresponds in intensity with that of the blood of the normal infant in the first four months of life. In 41, or 19.4 per cent, of the 211 observations in table 1 which showed moderate or marked degrees of decolorization the reaction was regarded as marked, or 4 plus. On the other hand, of the 108 observations for the children with nutritional anemia which showed moderate or marked decolorization, the reactions in 73, or 67.6 per cent, were designated as 4 plus.

Cases illustrating decolorization by the blood of children with nutritional anemia are shown in table 4. In the case of D. F., 3 plus decolorization may be noted with an accelerated sedimentation rate of 15 mm. and a subnormal hematocrit value of 26 per cent. In the case of P. L., 4 plus decolorization may be noted with hematocrit values of 32 to 35 per cent, although the sedimentation rates were normal. In the case of W. W., maximum decolorization was noted on December 4, the eighth day after the institution of iron therapy, when a hematocrit reading of only 26 per cent was recorded. The same degree of decolorization was noted four days later, with an improved, though subnormal, hematocrit value. In the case of H. A., 4 plus decolorization occurred five days after the institution of iron therapy, with a sedimentation rate of 32 mm. and a hematocrit value of only 18 per cent. When the latter rose to 30 per cent and the sedimentation rate slowed to 18 mm., both still subnormal values, decolorization remained intense. In the case of C. B., similarly, moderate decolorization occurred with a rapid sedimentation rate of 20 mm. and hematocrit values of 28 and 27 per cent.

In the cases of J. D. and M. T., anemia was complicated by tonsillitis and infections of the upper respiratory tract, respectively. Despite rapid sedimentation rates, for J. D. on January 14, 15 and 23 and for M. T. on June 1, 8 and 12, moderate and marked adsorption of methylene blue occurred after iron therapy.

Adsorption of the dye after iron therapy was also noted in other cases in which there was iron deficiency, when there was an accompanying low grade infection and the sedimentation rates were accelerated. In cases, however, in which there was severe infection, accompanied by a sharp and persistent febrile reaction, decolorization of the dye did not occur, despite antianemic therapy.

TABLE 4.—*Examples of Changes in Adsorption of Methylene Blue in Cases of Nutritional Anemia*

Case No.	Patient	Age	Date	Adsorption, Degree of Decolorization	Sedimentation Rate, Mm. in 1 Hr.	Hemoglobin in Whole Blood, Gm. per 100 Cc.	Red Blood Cells: Million per Cu. Mm.	Red Blood Cells: Volume of Packed Cells, Cc. per 100 Cc.
1	D. F.	14 mo.	6/20/36	3	15	6.0	3.84	26
			6/20/36	Ferrous sulfate, 8 grains daily				
			6/25/36	4	8	7.4	3.48	30
			7/ 7/36	4	5	11.0	4.65	39
			7/ 7/36	Ferrous sulfate, 12 grains daily				
			7/28/36	4	7	12.2	4.46	38.5
			7/28/36	Iron therapy discontinued				
			9/22/36	3	7	12.2	3.93	38
			9/22/36	Ferrous sulfate, 6 grains daily				
			11/ 5/36	3	6	13.0	4.05	42
2	P. L.	11 mo.	5/15/37	4	9	8.0	4.51	32
			5/15/37	Ferrous sulfate, 8 grains daily				
			5/18/37	4	10	8.0	4.28	32
			5/20/37	4	6	9.0	4.80	35
			5/22/37	4	9	9.0	4.50	36.5
			5/27/37	4	6	11.8	4.41	40
3	W. W.	16 mo.	11/26/36	0	17	3.0	1.70	12
			11/27 and 11/28/36, transfusions					
			11/27/36	Ferrous sulfate, 12 grains daily				
			11/29/36	0	15	4.8	2.64	19
			12/ 4/36	4	10	6.4	3.11	26
			12/ 8/36	4	6	8.4	3.69	32
			12/16/36	4	5	11.4	4.25	40
			12/29/36	4	4	12.6	4.62	42
4	H. A.	3 yr. 5 mo.	12/11/37	0	40	4.0	2.025	14
			12/14/37	Ferrous sulfate, 12 grains daily				
			12/19/37	4	32	5.0	2.350	18
			12/26/37	4	18	8.0	2.870	30
			12/31/37	4	11	10.0	3.470	35
			1/ 7/38	3	7	13.0	4.020	40
5	C. B.	6 yr.	10/ 7/36	3	20	7.0	3.03	28
			10/14/36	3	20	6.5	2.99	27
			10/14/36	Iron and ammonium citrates, 48 grains daily				
			10/28/36	3	8	9.0	3.05	32
			10/30/36	4	8	9.6	3.48	32
			11/ 4/36	Iron and ammonium citrates, 90 grains daily				
			11/ 5/36	4	8	10.0	3.54	34
			11/ 7/36	4	4	10.0	3.58	35
			11/14/36	4	4	12.0	4.11	40
6	J. D.*	2 yr.	12/27/35	0	27	9.0	4.59	30
			12/31/35	Iron and ammonium citrates, 45 grains daily				
			1/ 5/36	2	28	9.0	4.79	33
			1/10/36	Iron and ammonium citrates, 90 grains daily				
			1/14/36	3	24	10.0	5.15	38
			1/15/36	3	25	10.4	4.71	36
			1/23/36	4	15	11.4	5.28	41
			1/25/36	4	12	12.0	4.73	40
7	M. T.*	19 mo.	5/29/37	0	29	7.0	3.49	30
			5/29/37	Ferrous sulfate, 8 grains daily				
			6/ 1/37	3	30	7.8	3.60	33
			6/ 8/37	3	20	10.0	4.43	37
			6/12/37	4	19	11.2	4.40	40
			6/19/37	4	12	12.8	4.27	43
			6/24/37	4	9	12.8	4.60	42
			7/ 1/37	4	8	12.8	4.32	42

* Patients had nutritional anemia complicated by infection.

MECHANISM OF ADSORPTION OF METHYLENE BLUE

In the previous study it was shown that the erythrocyte constitutes the essential factor concerned in the decolorization process. Neither the other formed elements nor the serum or plasma was found to be capable of adsorbing methylene blue unaided. The capacity of the erythrocyte for adsorption of the dye was repeatedly confirmed, as illustrated by the following typical observation: A sample of blood which has removed the dye from the solution in the cold may be washed several times with cold citrate solution, and each washing will clear. When the sediment of red cells is then mixed with citrate solution and exposed to warm temperature, the dye will reappear in strong concentration in the supernatant layer.

The mechanism of this reaction was subjected to more intensive study by the following procedure: The blood of 42 subjects included in the present investigation was examined in 61 groups of observations. When the blood was obtained for the usual methylene blue and sedimentation tests, as already described, an additional specimen of capillary or venous blood was introduced into a tube containing either heparin or a small quantity of a 3 per cent solution of sodium citrate. After preliminary removal of the heparinized or citrated plasma by centrifugation for one minute at 2,500 revolutions per minute a 50 per cent suspension of the cells was made with a 3 per cent solution of sodium citrate. One-tenth cubic centimeter of this sample was mixed with 0.1 cc. of solution of dye of the concentration employed in the present study (3:100,000) and transferred to the narrow tubes used in the tests. After the fluid had stood overnight in the ice box, the depth of color above the sedimented layer was noted. In experiments of this type decolorization usually occurred, regardless of whether or not decolorization took place in the usual test with unaltered blood. When the remaining sample of the heparinized or citrated fresh blood was subsequently washed with a large quantity of citrated solution and centrifuged for five minutes at the same speed the results were different. After this more prolonged centrifugation, a 50 per cent suspension of the red blood cells was again made up, admixed with a solution of methylene blue in 0.1 cc. proportions, transferred to small tubes and placed in the ice box for sedimentation overnight. The supernatant layer in every case was blue, which indicated that no adsorption had taken place, in contradistinction to active decolorization when the blood was subjected to the initial short period of centrifugation.

This observation led to the conclusion that some substance was removed in the course of washing which was essential to the decolorization reaction or that the red blood cells had been altered. Microscopic examination, however, revealed structurally unchanged

erythrocytes. It was subsequently determined that decolorization could be restored when there was added to the solution of dye in the test tube a drop of either the plasma or the serum of the same or of any normal subject or a drop of serum from a guinea pig, horse or rabbit. The greater degree of decolorization usually occurred with the subject's serum rather than with plasma, and citrated plasma was found to be superior to that which was heparinized. The most intense decolorization occurred, however, with the serums of the other species. With these, the supernatant layers often showed complete decolorization, possessing the clarity of water, regardless of the degree of the reaction with the usual methylene blue test on whole blood. It was shown, furthermore, that the serums of the different species were potent in the fresh state or when thay had previously been heated to 56 C. for one-half hour. The hemolysis noted by Ponder [6] when the serum was added to red blood cells sensitized by brilliant green did not occur in these studies. Investigation in the present experiment revealed that lysis was prevented because of the low temperatures employed.

The role of fibrinogen having been eliminated by the observation that serum not only could be substituted for plasma but was often superior to it, the other fractions of serum were subjected to analysis. The albumin and globulin components of the serum of 1 of the human subjects and of a guinea pig were obtained by differential precipitation with sodium chloride and subsequent dialysis. In only 4 tests of a large number did concentrated globulin from the human subject restore decolorization. In the large majority of instances, neither this component nor a combination of the two was as effective in producing decolorization of methylene blue as the original serum. Since serum was ordinarily effective as plasma in restoring decolorization, and usually more so, it may be stated that the erythrocytes adsorb the dye from a solution only in the presence of a trace of intact serum. It may be added that a 3 or a 6 per cent solution of egg albumin could not be substituted for serum or plasma. In no instance did the various types of plasma or serum or their components in any concentration decolorize methylene blue. The decolorizing component of the blood resided solely in the red cells.

That the dye is adsorbed by the stromal constituent of the cell, which includes its membrane and exists in loose combination with it, is illustrated by the following observation: Blood was admixed with a solution of methylene blue as in the tests, and the supernatant layer

6. Ponder, E.: (*a*) The Mammalian Red Cell and the Properties of Haemolytic Systems, in Chambers, R.: Protoplasma-Monographien, Berlin, Verlag von Gebrüder Borntraeger, 1934, vol. 6, p. 246; (*b*) Haemolysis by Brilliant Green and Serum, Proc. Roy. Soc., London, s.B **103**:556 (Nov.) 1928.

was removed after exposure to the cold for twenty-four hours. The cellular sediments of several tubes were combined and thoroughly mixed with a 3 per cent solution of sodium citrate, and the suspension was divided into two equal portions. One portion was washed three times with a cold solution of sodium citrate; as each washing was removed it was noted to be colorless, except the first, which contained at times faint traces of an excess of methylene blue. The second fraction was treated differently in that it was first exposed to a temperature of approximately 37 to 40 C. for fifteen minutes or was kept at room temperature overnight. After centrifugation the fluid layer possessed a deep blue color, while the sediment consisted of intact red blood cells. Washing was repeated twice, each time with preliminary exposure to warm temperatures. The washings were still blue, but not as deeply tinted as the initial one.

Each of the two washed fractions, the one in which the cellular sediment was washed with cold citrate and the one which was exposed to the warmth, was hemolyzed by the addition of distilled water. After hemolysis was completed, the stromal elements were thrown down by centrifugation at high speed and washed several times with a cold 3 per cent solution of sodium citrate. Comparison of the two sediments of stromas was striking. Whereas the residuum from the cells washed in the cold solution consisted of a heavily pigmented blue-green mass, that derived from the cells exposed to higher temperatures was either entirely colorless or contained only a few minute particles of the dye.

It is possible, of course, that after red blood cells have been admixed with methylene blue, some of the dye also penetrates the cells, to be combined with hemoglobin and to be liberated after the exposure to higher temperature or after hemolysis. On the other hand, the evidence is unequivocal that the dye is in large part adsorbed by the stroma. A portion of the latter may be situated in the interior of the red blood cell according to some investigators, although the bulk of stroma is probably derived from the outer limiting membrane of the cell.[7] It is from this site that the dye is released when the temperature is elevated. In the limited number of observations in which the pigmented stroma was studied, the dye diffused from it very slowly in the warmth as compared with its rapid liberation from the intact red blood cell.

In the course of these experiments it was also noted that even in the tests in which solutions of methylene blue are not apparently decolorized, as in case of active disease, when the blood cells sediment

7. Jorpes, E.: The Protein Component of the Erythrocyte Membrane or Stroma, Biochem. J. **26**:1488, 1932.

rapidly, a small quantity of the dye is always adsorbed by the red blood cells. Similarly, exposure of the red blood cells to solutions of methylene blue at room temperatures results in slight adsorption of the dye, a fact which may be readily demonstrated by subsequent exposure of the washed sediment to temperatures of 37 C. or above.

COMMENT

Methylene blue, a quinoid dyestuff, tetramethylthionine, contains no oxygen in its molecule. It is reduced to a colorless or leukocompound when its chromophore groupings combine with hydrogen, and on subsequent oxidation the original color is restored. The reaction described in this paper cannot, however, be accounted for by purely chemical changes but may be more readly explained as due to the operation of a well known physical phenomenon.

In a routine test, capillary blood is mixed with a dilute solution of methylene blue and interaction is permitted to take place during exposure overnight to ice box temperature. In the case of a healthy subject, at the end of this time a decrease in concentration of the blue color is usually noted in the fluid layer above the sedimented cells. In the instances in which complete decolorization has taken place attempts at oxidation of the clear layer with strong oxidizing reagents fail to reveal the presence of the leukocompound. When the sedimented layer, however, is washed with cold citrate solution one or more times and the cells are resuspended in citrate solution at room temperature, the methylene blue reappears in strong concentration in the fluid layer. The absence of the dye from the supernatant layer and its release from the red blood cells suggest that the dye has been removed from the solution by adsorption. The red blood cells that have decolorized the solution of methylene blue are intact when examined under the microscope, even though they have been subjected to several washings, which require repeated centrifugation. That their appearance gives no evidence of their having taken up dye is due to the minute quantities of methylene blue that have been adsorbed by the extensive surface area of the red blood cells.

In the previous study it was shown that when the dye was removed by the red blood cell under the experimental conditions specified methylene blue was not chemically altered. Had the process by which the solution was decolorized involved a phase of biologic oxidation, the dye would have served either as a passive indicator or as an active respiratory catalyst, and intermediary compounds, such as leukomethylene blue and methemoglobin, would have been formed. It has already been shown, however, that the leukocompound did not occur, and spectroscopic examination failed to reveal the presence of methemoglobin. Furthermore, the formation of the latter would have

been interfered with by the low temperatures and the alkalinity of the medium required for the test under consideration.[8] The evidence points, therefore, to the adsorption of chemically unaltered methylene blue by the red blood cell.

There are several physical principles involving surface reactions that explain the decolorization of solutions of methylene blue by red blood cells under the prescribed conditions. The Gibbs principle with regard to changes in tension at surfaces has been expressed by Bayliss[9] as follows:

> Any process that diminishes the free energy at an interface will tend to take place, whatever be the nature of the energy concerned, whether mechanical, electrical, chemical or other. If the surface has an electrical charge, a process diminishing it will be favored. If it possesses chemical energy, a reaction reducing this energy will take place, if possible, and so on.

In the phenomenon under consideration, free energy on the surface of the red blood cell is presumably reduced after the deposition of particles of methylene blue on the surface, with which the dye is in contact. Adsorption is also favored by the diminution of electrical energy, which probably occurs at the surface as a result of the interaction between the negative electrical charge borne by the red blood cell[10] and the positive charge of methylene blue.[11] This corresponds to the changes which take place when the negatively charged adsorbent kaolin takes up methylene blue.[12]

Decolorization of solutions of methylene blue in the cold and release of the dye from the red blood cell when it is exposed to higher temperatures also conform to established physical laws. It is known that the amount of adsorption increases with decreasing temperature.[13] According to Ponder,[14] since surface tension is lowered with a rise in temperature, the effect of a substance in reducing energy at a surface will be lessened with elevation of temperature. Dissociation of adsorption compounds, therefore, occurs with an increase in temperature, as is known. The reduction in surface tension associated with a rise

8. Brooks, S.: The Oxidation of Haemoglobin to Methaemoglobin by Oxygen, Proc. Roy. Soc., London, s.B **109**:35 (Sept.) 1931.

9. Bayliss, W. M.: Principles of General Physiology, ed. 4, New York, Longmans, Green & Company, 1924, p. 55.

10. Jorpes,[7] Fahraeus, R.: The Suspension Stability of the Blood, Physiol. Rev. **9**:241 (April) 1929.

11. Ponder, E.: Essentials of General Physiology, New York, Longmans, Green & Co., 1929, p. 12.

12. Freundlich, H.: Colloid and Capillary Chemistry, translated by H. S. Hatfield, ed. 3, New York, E. P. Dutton & Company, 1926, p. 209.

13. Taylor, H. S.: A Treatise on Physical Chemistry, ed. 2, New York, D. Van Nostrand Company, Inc., 1931, vol. 1, p. 344.

14. Ponder,[11] p. 21.

in temperature causes the particles of methylene blue that have been concentrated on the surface of the red blood cell in the cold to be released, and the color reappears in the solution.

It has been repeatedly shown that relatively more of the substance is adsorbed from a solution of low concentration than from one of high concentration. This law of adsorption has been demonstrated in various ways, such as in the adsorption of dyes, of agglutinins by bacteria and of hemolysins by red corpuscles. The employment of extremely dilute solutions of methylene blue permitted the detection of gross variations in the concentration of dye which remained in the supernatant layer after admixture with blood. The fact that more than one supplement of dye may be adsorbed by the red blood cells but that soon a limit is reached when no further decolorization occurs is in accord with the physical phenomenon of the saturation of adsorbing surfaces.

The interaction of methylene blue with red cells and the alterations in surface tension that are brought about have a counterpart in other physical reactions. With gases, increased adsorption has been observed during a drop in temperature. Many immune reactions reveal similar characteristics, and the exposure to the cold is utilized practically. It has been possible, for instance, to remove the toxic effects of immune rabbit serum by its admixture with kaolin in the cold.[15]

A striking analogy is found between the phenomenon of cold agglutination and that of adsorption of methylene blue. Landsteiner[16] showed that when animal or human red blood cells are mixed with a sufficient quantity of the homologous serum and kept at ice box temperature agglutination of the cells occurs. When the agglutinated masses are washed with ice-cold saline solution and are resuspended in saline solution at room or at a warmer temperature the clumps break up. The release of the cold agglutinin in the supernatant fluid is revealed by the clumping which again results when the fluid is mixed with fresh blood and exposed to the cold. This phenomenon is exaggerated in certain pathologic conditions, notably paroxysmal hemoglobinuria.

Further studies are required to determine whether substances other than methylene blue and cold agglutinins are adsorbed by the red blood cells. If immune bodies, for example, react in the same manner, this temperature sequence might be employed to advantage with serum therapy. In conditions for which both giving of specific serums and

15. Goodner, K.; Horsfall, F. L., Jr., and Dubos, R. J.: Type-Specific Antipneumococcic Rabbit Serum for Therapeutic Purposes, J. Immunol. **33**:279 (Oct.) 1937.

16. Landsteiner, in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 898.

transfusion of blood are indicated, it may be desirable to supplement their separate administration by one of blood and immune serum which have previously been admixed and exposed to the cold. Possibly immune bodies may be more slowly released from the sensitized red blood cells at body temperatures, to give a prolonged therapeutic effect as compared with the rapid and immediate action obtained when immune serum enters the blood stream directly.

The fact that 50 per cent supensions of red blood cells always decolorized methylene blue, provided traces of serum were present, regardless of the results of initial tests with whole blood, was to be expected. The greater adsorptive surface provided by the 50 per cent suspension of cells required for the former tests as compared with the lower cell volume found in whole blood, together with the smaller amounts of methylene blue employed (0.1 cc. as compared with 0.2 cc. in the routine tests), assured adsorption of the dye in the presence of serum. In addition, sedimentation proceeded slowly, since the red cells were washed free from plasma, with removal of the factors which in pathologic states accelerate sedimentation.

The observation that a trace of serum is an essential factor in the adsorption of the dye by the red blood cells suggests that preliminary preparation of the red blood cell is required, the process corresponding to antigenic changes in immunologic reactions. In the reaction between the red blood cell and its environment, the cell membrane, as already indicated, stands in a relation of primary importance. While no envelope has been histologically identified for the red blood cell, its semipermeable membrane contains a protein, stromatin, and the lipoids lecithin and cholesterol.[17] In adsorptive phenomena, however, not only the chemical structure but the physical state of the outer rim of the red blood cell must be considered. For example, the tendency of red blood cells to aggregate, represented by formation of rouleaux, depends on a reaction between constituents of the plasma and the surface forces of the red blood cell. Oliver and Barnard [18] have shown that when red blood cells are suspended in a fluid, their electrokinetic properties may be better explained as due to a surface of globulin than to one of albumin or lipoid. In an analysis of the action of opsonin and bacteriotropin it has been shown [19] that when antigen is admixed with homologous serum its surface is prepared for phagocytosis by

17. Ponder, E.: The Kinetics of Hemolysis, Physiol. Rev. **16**:19 (Jan.) 1936.

18. Oliver, J., and Barnard, L.: The Nature of the Surface of the Red Blood Cell and Mechanisms of Suspension Stability, Am. J. Physiol. **73**:401 (July) 1925.

19. Strumia, M.; Mudd, S.; Mudd, E. B. H.; Lucke, B., and McCutcheon, M.: On the Mechanism of Opsonin and Bacteriotropin Action, J. Exper. Med. **52**:299 (Sept.) 1930.

the deposition of substances derived from the globulin fraction of the antiserum. Similarly, the function of the serum required for decolorization of a solution of methylene blue may also be to prepare the surface of the red blood cell for the adsorption of dye. It has been shown [19] that bacteriotropic and surface effects of the globulin fractions of immune serum are not appreciably weakened by preliminary heating of the serum. In the present study, also, fresh as well as heated serums were effective in decolorization.

The results reported in this paper have shown that with the experimental procedure employed the red blood cells of infants and children remove methylene blue from dilute solutions in varying degrees. It was observed that a minimum of adsorption occurred with the blood of sick children as compared with the moderate and marked degrees noted with the blood of healthy subjects. The variations observed could in general be correlated with the rapidity with which the red blood cells settled out of the tubes containing the dye. Although exposure at ice box temperatures retarded the rate of sedimentation, nevertheless in case of active disease this tendency was overcome by the acceleration characteristic of disease. As compared with the slower rates for the healthy subject, the increased rate of sedimentation associated with infection afforded the erythrocytes a negligible opportunity for removal of the dye in which they were suspended. With blood removed during convalescence or from healthy subjects, the more prolonged periods of exposure of the red cells to the dye because of normal sedimentation rates resulted in increased adsorption of the dye. In several instances, however, samples of blood were observed to sediment at parallel rates over a period of several hours; yet the degree of decolorization in the tubes was unequal. These observations suggest that erythrocytes possess individual capacities of adsorbing dye. In pathologic states the erythrocyte may conceivably undergo qualitative changes, as indicated by a diminished capacity for decolorization, similar to the better known alterations in its numbers, size, shape and hemoglobin content.

This hypothesis is strengthened by the observations in the cases of nutritional anemia. The unusual intensity of decolorization associated with this condition may be due in large part to the sluggish manner in which dilute suspensions of red blood cells sediment, which affords increased opportunities for exposure to the dye. Qualitative changes were suggested, however, in the cases in which rapid rates of sedimentation were accompanied by moderate and marked degrees of decolorization. In the cases in which reticulated red blood cells were counted maximum decolorization was observed in many instances, irrespective of the degree of reticulocytic response. However, other distinctive properties of young red blood cells may account for the completeness with which the solution of dye is decolorized. Of these, the stickiness

of the envelope, designated by Key [20] as a characteristic of young red blood cells, may contribute to the active removal of particles of methylene blue suspended in citrate solution.

The tests as outlined required further refinements of technic to permit their use as a measure of alteration of the decolorizing capacity of the red blood cell in various clinical conditions. Further studies are necessary, for example, to determine to what extent variations in decolorization, as measured by the reaction, reflect changes in the adsorptive function of the red blood cell for substances other than methylene blue. However, even with the test described in this paper, the reactions at the two extremes may serve as reliable end points for clinical application: namely, the complete absence of decolorization, with a deep blue supernatant layer, and the complete removal of the dye, leaving a colorless layer. It may be stated that the complete absence of decolorization in a test indicates the presence of a pathologic condition, while maximum or complete decolorization suggests that recovery is in progress. In both instances, the sedimentation rate and the white blood cell count may yield borderline readings. Also, since marked decolorization of methylene blue solution is encountered in cases of uncomplicated iron deficiency anemia among infants and children, the test may prove helpful in making possible a more accurate diagnosis during the early stages of this condition.

As already stated, the results of the tests and the analysis of the mechanism of the reaction suggest that the red blood cell withdraws methylene blue from solution by adsorption. While the experimental conditions by which adsorption was demonstrated differ from those in circulating blood, the behavior of the red blood cell in this reaction suggests a basis for related physiologic phenomena. When the test is carried out at room temperature, a small amount of dye is adsorbed by red blood cells; this is retained after washing and is released by subsequent heating. The quantity is considerably less, however, than when the mixture of dye and blood is first exposed to cold, as described in this study. Ponder [6b] observed that when brilliant green was added to red blood cells at 15 C. a loose union was formed between the dye and the cells, as evidenced by the fact that warming the sensitized cells to 37 C. resulted in liberation of the dye. Similarly, reports are available to show that at higher temperatures the dye vital red is adsorbed by the red blood cells of the ox and the dog [21] and methylene blue by the red blood cells of the rabbit.[22]

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20. Key, J. A.: Studies on Erythrocytes, with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch. Int. Med. **28**:511 (Nov.) 1921.

21. Lindhard, J.: Dye Methods for Determining the Blood-Volume Tested in Vitro, Am. J. Physiol. **76**:496 (May) 1926.

22. Iwanowsky, N., and Sabolotnowa, M.: Ueber die Adsorptionsfähigkeit der Erythrocyten: Adsorption von Methylenblau, Biochem. Ztschr. **216**:130, 1929.

The results of studies are available which have shown that red blood cells adsorb substances other than dyes, among these diphtheria toxin,[23] hormones [24] and strychnine.[25] It may well be that adsorptive processes are partially responsible for the deposition on the surface of the red blood cell of many other substances with which it may be in contact in the plasma and for their subsequent passage through the blood stream. The quantity attached to the surface of the red blood cell is probably minimal as compared with that free in the plasma. There are undoubtedly metabolic, immune and endocrine products of which the mode of transport through the blood stream, although it has not been entirely accounted for, may, in part at least, be explained by the mechanism described for methylene blue. This possibility is further suggested by the extensive surface provided by the red blood cells, which has been estimated by Starling [26] as 3,000 square meters for a man of 70 Kg. On the basis of the behavior of other substances,[25] it is also possible that materials fixed by the stroma of the red blood cells are more slowly released and therefore do not exert their action as promptly as those dissolved or suspended in the plasma. As these studies have indicated, the type of substance, the quantity taken up by the red blood cell and its subsequent liberation will depend ultimately on a great many physicochemical relations which control the reaction between the particular substance and the red blood cell membrane.

SUMMARY

In a previous study it was shown that when the blood of a healthy infant was mixed with a dilute solution of methylene blue in sodium citrate and exposed to the cold the solution was rapidly decolorized. This reaction proceeded most actively during the first four months of life.

Investigation revealed that the red blood cells were the elements of the blood responsible for decolorization and that the dye was removed from the solution by the process of adsorption. Exposure of the washed cellular sediment to higher temperatures after decolorization in the cold resulted in reappearance of the dye in the surrounding medium.

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23. Glausmann, M. P.: Ueber die Adsorptionsfähigkeit der Erythrocyten und die Diphtherie Immunität, Biochem. Ztschr. **177**:309, 1926. Dujarric de la Rivière, R., and Kossovitch, N.: Globules rouges et immunité: Adsorption des toxines par les globules rouges, Compt. rend. Soc. de biol. **110**:284, 1932.

24. de Gedroyć, M.: Méthode biologique de concentration des hormones des liquides et tissus organiques, Compt. rend. Soc. de biol. **114**:338, 1933.

25. Weiss, S., and Hatcher, R. A.: Studies on Strychnin, J. Pharmacol. & Exper. Therap. **19**:419 (July) 1922.

26. Starling, E. H.: Principles of Human Physiology, ed. 6, Philadelphia, Lea & Febiger, 1933, p. 700.

The present investigation consisted of an extension of the study of this phenomenon with the blood of older infants and children. A test was devised in which measured amounts of capillary blood and of a dilute solution of methylene blue were thoroughly admixed and exposed to ice box temperature overnight. The depth of color remaining in the overlying column of fluid after the red blood cells had settled out was matched with appropriate standards. These ranged from a solution of deep blue color, in which little or no adsorption had occurred, to one with the clearness of water, from which the dye had been completely removed.

Although the rate of sedimentation of red blood cells is retarded in the cold, it was soon apparent that the extent of decolorization varied directly with the length of time the cells were in contact with the particles of methylene blue in the mixture. The greater this period, that is, the slower the rate at which the cells settled out, the greater was the degree of decolorization; conversely, the more rapid the rate, the more dye was left in the supernatant layer. Because of this relationship, sedimentation tests were carried out at room temperature with all dye tests.

A total of 576 tests on decolorization of methylene blue, with simultaneous determinations of the volume of packed red blood cells and of the sedimentation rate, were carried out for 227 infants and children ranging in age from 5 months to 14 years.

There were several groups of subjects: one of well children, another of children with nutritional anemia who were undergoing treatment with iron and a third, the largest, of children with a variety of pathologic disorders, usually of an infectious nature, whose blood was studied periodically from the acute stage of illness through convalescence. For all of the groups the degree of decolorization was compared with the sedimentation rate, and in the cases of anemia with the hematocrit value as well.

The degree of adsorption by the red blood cells as measured by the decolorization of the solution of methylene blue was found to be closely correlated with the average sedimentation rate, although there was a significant range of variation within each group of tests. As a general rule, decolorization was at a minimum during the stage of acute illness and returned during defervescence and recovery.

In 91 per cent of 89 observations on 64 well children the intensities of decolorization were moderate or marked. In cases of the children with infections, during the stage of acute illness, in 92 per cent of 146 observations the blood did not decolorize the solution of methylene blue, and at the same time the sedimentation rate was rapid. Of 211 observations on subjects with moderate or marked decolorization, normal sedimentation rates occurred in 71 per cent. The exceptions occurred

in tests for patients who had passed the acute phase of their illness and were recovering or who were ambulatory with mild infections. In these tests judgment as to the clinical status was often uncertain; the white blood cell count often fell within the normal range, and the sedimentation rates were accelerated to a moderate degree only.

Of all the groups studied, the most marked decolorization was noted in the case of infants and children with uncomplicated nutritional anemia who were receiving iron therapy, regardless of their hematocrit levels or sedimentation rates. This characteristic of the blood was further emphasized by an analysis of the number in this group whose blood showed a maximal, or 4 plus, degree of decolorization. Of 211 observations for the nonanemic group, with moderate or marked degrees of decolorization, 19.4 per cent showed maximal decolorization, whereas of 108 observations for the group with nutritional anemia, 67.6 per cent showed the maximal degree of decolorization.

In an analysis of the mechanism by which red blood cells react with methylene blue, it was observed that, although decolorization is accomplished solely by adsorption of the dye by the red blood cell the presence of a trace of serum or of plasma was an essential element of the reaction. It was found that fresh or heated plasma or serum of the same or of any other normal subject or serum from the guinea pig, horse or rabbit could be utilized interchangeably. A drop of serum or plasma could restore the capacity of the red blood cells to adsorb methylene blue after the plasma had been thoroughly removed from them by several washings. On the other hand, the plasma or serum in itself could not in any proportions decolorize the solution of dye in the cold.

It was shown that when methylene blue is adsorbed it is attached to the stroma of the red blood cells. Liberation of the dye from the deeply pigmented blue-green stromal residuum obtained from these cells after hemolysis is slow as compared with the rapid diffusion from the intact red blood cells as the temperature is elevated.

Decolorization of solutions of methylene blue by red blood cells under the experimental conditions outlined can in no way be interpreted as an oxidation-reduction phenomenon. The adsorption of chemically unaltered dye by the intact red blood cell in the cold and its release in the warmth conform to well known physical laws. A striking similarity exists between the phenomenon of cold agglutination of the red blood cells and that of adsorption of methylene blue.

The phenomenon described, together with related evidence obtained from other sources, lends weight to the hypothesis that adsorption by the surface of red blood cells may enter into physiologic processes. The differential temperature reactions being disregarded, the adsorption of dye by the red blood cells as described in this study serves to illustrate

what may happen when the extensive surface presented by red blood cells is exposed to the diversity of substances which are dissolved or suspended in the plasma. Adsorption by red blood cells may account, in part at least, for the transport of metabolic, immune and endocrine products through the blood stream. The quantity attached to the red blood cell, however, is probably minimal as compared with that free in the plasma, and the substances fixed by the stroma are probably more slowly released than those in the plasma. How much of the material taken up by the red blood cell will subsequently be liberated will depend ultimately on physicochemical reactions between the particular substance and the membrane of the cell.

It is suggested that immune bodies be studied in the manner of methylene blue in order that their adsorption at various temperatures by red blood cells may be observed, with the possibility of a practical application in serum therapy.

The methylene blue tests as outlined require further refinements of technic before they can be employed as a routine. In their present state, however, particularly when results of other laboratory tests are equivocal, the reaction at either extreme may be of value, namely, the complete absence of decolorization with active disease, on the one hand, and the presence of a completely decolorized supernatant layer, as indicative of the recovery process, on the other. Furthermore, marked decolorization by the blood of subjects with uncomplicated nutritional anemia may serve as an additional aid to diagnosis of this condition.

Further study may reveal that the red blood cells, besides being influenced grossly in their affinity for methylene blue by their rate of settling, may possess individual capacities for adsorption of dye, as suggested by several observations in this study. It remains to be determined to what extent the degree of adsorption of dye by red blood cells under the specified experimental conditions constitutes a measure of the adsorptive capacities of the red blood cell for unrelated substances.

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INTRACUTANEOUS TESTS FOR DETERMINING SUSCEPTIBILITY TO WHOOPING COUGH

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Since 1921 the literature has contained articles of interest on the subject of cutaneous testing for early diagnosis of whooping cough and for determining susceptibility or immunity to the disease. The reported results have been conflicting.

In 1934 Siebler and Okrent [1] reported on a series of 186 subjects tested intracutaneously. The vaccine was prepared according to Sauer's technic (1933).[2] It was found that 76 per cent of the subjects with a history of whooping cough gave negative cutaneous reactions and, conversely, that 80 per cent of those with no history of whooping cough had positive reactions. The readings were made after seventy-two hours.

On the other hand, Paterson, Bailey and Waller (1935),[3] also using Sauer's vaccine, reported that children with a history of pertussis usually had positive cutaneous reactions, connoting immunity to the disease, while those with no history of whooping cough had negative reactions. The readings were made at twenty-four, forty-eight and seventy-two hour intervals. The cutaneous reactions became positive one week after the last injection, showing, the authors concluded, that in contrast to what Sauer claimed [4] for the vaccine, an allergic state is developed, which gives hypersensitiveness to the skin three or four weeks after the initial dose of vaccine, causing a positive reaction. Later Paterson [5] reported that the results varied according to the batch of vaccine used. O'Brien [6]

1. Siebler, S. K., and Okrent, S. J.: Pertussis: Determination of Immunity by Means of Cutaneous Test, J. Pediat. **4**:188-190 (Feb.) 1934.

2. Sauer, L. W.: Whooping Cough: A Study in Immunization, J. A. M. A. **100**:239-241 (Jan. 28) 1933.

3. Paterson, D.; Bailey, R. H., and Waller, R. G.: Control of Whooping Cough with Serum and Vaccine: Uses of New Skin Test, Lancet **2**:361-364 (Aug. 17) 1935.

4. Sauer, L. W.: Immunization with Bacillus Pertussis Vaccine, J. A. M. A. **101**:1449-1453 (Nov. 4) 1933.

5. Paterson, D.: Skin Tests for Whooping Cough, Lancet **2**:1207 (Nov. 23) 1935.

6. O'Brien, B.: Intradermal Tests for Susceptibility to Whooping Cough, Lancet **1**:131-132 (Jan. 16) 1937.

tested 371 children similarly, and his results agreed with those of Paterson.

Paton [7] made a study of the complement fixation test in confirming the clinical diagnosis of whooping cough and found it to be of value. He used this test as a control in the study of intradermal tests and found no correlation between them. A high percentage of patients with whooping cough gave positive reactions, but so did a group of control patients with no history of previous infection.

The purpose of the present study was to investigate the reliability of cutaneous tests for determining susceptibility to whooping cough. The plan was to test children who were supposedly susceptible to the disease to see if any uniform reactions could be obtained by the intradermal injection of small quantities of pertussis vaccine. After the results were noted the subjects were inoculated with pertussis vaccine, as Sauer prescribed for immunization. Sauer [4] claimed that after vaccination there is gradually increasing immunity, which is complete in about four months. If this is true and if the reaction to the cutaneous test is a reliable index to susceptibility or immunity, one would expect the reaction to be altered after vaccination. Our cutaneous tests were therefore repeated at various intervals after complete treatment for immunization.

SUBJECTS

The subjects for this study were selected from the Children's Dispensary of the Germantown Hospital. The ages ranged from 9 months to 12 years, the majority being under 3 years. The results are reported in two groups, as the materials and the methods varied somewhat. It will be noted that 7 of the children in the first group had had whooping cough. None of the other children in either group gave a history which would lead one even to suspect previous infection with pertussis.

MATERIALS AND METHODS FOR GROUP 1

The following materials were used:

1. Pertussis vaccine prepared by the National Drug Company, containing 10,000,000,000 organisms per cubic centimeter. This is prepared from freshly isolated hemolytic strains of Haemophilus pertussis. Organisms are grown for forty-eight hours on agar containing freshly defibrinated human blood. The growth is washed from the surface of the medium and mixed with a 1:10,000 dilution of merthiolate in a physiologic solution of sodium chloride.

2. A 1:10,000 dilution of merthiolate in a physiologic solution of sodium chloride, used as control.

3. Dilute pertussis vaccine, containing 1,000,000 organisms per cubic centimeter. This was used to determine whether the number of organisms per cubic centimeter of material injected altered the reaction.

In each case 0.1 cc. of each material was injected intradermally on the flexor surface of the forearm. The readings were taken seventy-two hours later.

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7. Paton, J. P. J.: The Diagnosis of Whooping Cough, Lancet **1**:132-134 (Jan. 16) 1937.

TABLE 1.—*Results of Cutaneous Tests for Susceptibility to Whooping Cough: Group 1**

Patient	Tests Made Before Immunization			Tests Made After Immunization					
	P. V.	M.	D. P. V.	1 Mo. P. V.	2 Mo. P. V.	3 Mo. P. V.	4 Mo. P. V.	5 Mo. P. V.	6 Mo. P. V.
Patients with No History of Whooping Cough									
1	—	—	—	—	..	..	—	..	..
2	—	—	—	—	..	..	..	..	..
3	+	—	—	..	—	..	..	..	..
4	—	—	—	..	..	..	—	..	..
5	—	—	—	..	—	..	..	..	—
6	—	—	—	..	—	..	—	..	—
7	—	—	—	..	—	..	—	..	—
8	—	—	—	..	—	..	..	..	..
9	—	—	—	..	—	..	..	..	..
10	—	—	—	..	—	..	..	..	..
11	—	—	—	..	—	—	..	..	..
12	—	—	—	..	—	..	—	—	—
13	—	—	—	..	—	..	—	—	—
14	—	—	—	..	—	..	—	—	—
15	—	—	—	..	—	—	..	..	—
16	—	—	—	..	+	..	..	—	..
17	+	—	—	—	..	..	..	..	..
18	—	—	—	..	..	..	..	..	..
19	—	—	—	..	—	..	..	..	..
20	—	—	—	..	—	..	—	—	..
21	—	—	—	..	..	..	..	..	—
22	+	—	—	..	..	—	..	—	..
23	—	—	—	..	—	—	—	—	—
24	—	—	—	..	—	..	..	—	—
25	+	—	—	..	—	..	..	..	—
26	+	—	—	..	..	..	..	+	..
27	+	—	—	..	..	..	..	—	—
28	—	—	—	..	..	..	..	—	—
29	—	—	—	—	..	..	..	..	..
30	+	—	—	—	..	..	..	..	..
31	—	—	—	—	..	..	..	..	..
32	—	—	—	—	..	..	..	..	..
33	—	—	—	—	..	..	..	—	..
34	—	—	—	..	—	—	..	..	—
35	—	—	—	..	—	—	..	..	—
36	—	—	—	..	—	..	..	..	..
37	—	—	—	..	..	..	..	—	..
38	—	—	—	..	..	—	..	..	..
39	—	—	—	..	..	—	..	..	..
40	—	—	—	..	..	..	—	..	..
41	..	..	..	..	..	..	..	..	—
Patients with History of Whooping Cough									
42	—	—	—						
43	—	—	—						
44	—	—	—						
45	—	—	—						
46	—	—	—						
47	—	—	—						
48	—	—	—						

* "P. V." indicates pertussis vaccine (National Drug Company), of which 0.1 cc. was given intradermally; "M," merthiolate in a 1: 10,000 dilution, used as a control, of which 0.1 cc. was given intradermally; "D. P. V., dilute pertussis vaccine, containing 1,000,000 organisms per cubic centimeter, of which 0.1 cc. was given intradermally.

A positive reaction was recorded when the longest diameter of the area of redness was 1 cm. or more and a negative reaction if it was less than 1 cm. (This unit of measurement was decided on as a basis of comparison with the work of others who used the same unit. In the original tabulation accurate measurements were taken in millimeters, but for the sake of brevity the results are here recorded as negative or positive, though there was considerable variation in the size of the area of erythema and the amount of induration. For instance, invariably the reaction to merthiolate was negligible and the reaction to the dilute pertussis vaccine usually so, in comparison with the reactions obtained with vaccine of the full strength.)

After the testing the children were immunized with pertussis vaccine (National Drug Company), 1 cc. of the vaccine being injected into each arm; seven days later 1.5 cc. was injected into each arm and seven days after the second dose 1.5 cc., making a total of 8 cc.

Intradermal tests were repeated at various intervals after immunization in order that any alterations might be noted.

RESULTS IN GROUP 1

The experiment was completed on 48 subjects.[8]

The 7 who had had whooping cough previously had negative reactions to all three materials injected. The 41 previously uninfected children gave negative reactions to merthiolate and to dilute pertussis vaccine. With full strength pertussis vaccine given before immunization, 7 of the 41 "susceptible" subjects had positive reactions and the other 34 negative. After immunization the 7 who previously had positive reactions had negative reactions except 1 subject, who still had a positive reaction after five months. The 34 who previously had negative reactions continued to have them, with 1 exception. This subject had a positive reaction after two months and again had a negative reaction after five months.

MATERIALS AND METHODS FOR GROUP 2

The following materials were used:

1. Sauer's pertussis vaccine, prepared by Eli Lilly & Co., containing 10,000,000,000 organisms per cubic centimeter. The bacilli, grown for forty-eight hours in an incubator on cherry red Bordet medium, made with freshly defibrinated human blood, are scraped off and suspended in a 0.5 per cent phenolized saline solution.

2. A 0.5 per cent phenolized saline solution, used as a control.

3. Kreuger's undenatured bacterial antigen, 1 cc. representing 60,000,000,000 organisms. It is claimed that this preparation is free from nonspecific elements and contains native antigens in unaltered form, a result which is not possible with the preparation of vaccines.

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8. Only about half of the children immunized could be induced to return for retesting. Those who returned were irregular in attendance, as will be noted in the charts.

TABLE 2.—*Results of Cutaneous Tests for Susceptibility to Whooping Cough: Group 2**

Patient	Interval After Inoculation, Hr.	Tests Made Before Immunization			Tests Made After Immunization				
		P. V.	U. B. A.	S.	1 Mo. P. V.	2 Mo. P. V.	3 Mo. P. V.	4 Mo. P. V.	5 Mo. P. V.
1	24	—	—	—	..	..	+	..	..
	48	—	—	—	..	..	—	..	..
	72	—	—	—	..	..	—	..	..
2	24	+	—	—	..	..	—	..	..
	48	—	—	—	..	..	—	..	..
	72	—	—	—	..	..	—	..	..
3	24	+	—	—	..	..	..	..	..
	48	—	—	—	..	..	..	..	..
	72	—	—	—	..	..	..	..	..
4	24	+	—	—	..	+	..	..	..
	48	—	—	—	..	—	..	..	..
	72	—	—	—	..	—	..	..	..
5	24	—	—	—	..	+	..	..	+
	48	—	—	—	..	—	..	..	—
	72	—	—	—	..	—	..	..	—
6	24	+	+	—	..	+	..	..	..
	48	—	—	—	..	—	..	..	..
	72	—	—	—	..	—	..	..	..
7	24	—	—	—	..	..	..	..	..
	48	—	—	—	..	..	..	..	..
	72	—	—	—	..	..	..	..	..
8	24	+	+	—	..	+	..	..	+
	48	—	—	—	..	—	..	..	—
	72	—	—	—	..	—	..	..	—
9	24	+	—	—	..	+	..	..	+
	48	—	—	—	..	—	..	..	—
	72	—	—	—	..	—	..	..	—
10	24	+	+	—	..	+	..	..	+
	48	—	—	—	..	—	..	..	—
	72	—	—	—	..	—	..	..	—
11	24	+	—	—	..	+	..	..	+
	48	—	—	—	..	—	..	..	—
	72	—	—	—	..	—	..	..	—
12	24	—	—	—	..	..	..	..	+
	48	—	—	—	..	..	..	..	—
	72	—	—	—	..	..	..	..	—
13	24	—	—	—	..	..	+	..	..
	48	—	—	—	..	..	—	..	..
	72	—	—	—	..	..	—	..	..
14	24	—	—	—	..	..	—	..	..
	48	—	—	—	..	..	—	..	..
	72	—	—	—	..	..	—	..	..
15	24	—	—	—	..	..	+	..	..
	48	—	—	—	..	..	—	..	..
	72	—	—	—	..	..	—	..	..
16	24	—	—	—	..	..	..	+	..
	48	—	—	—	..	..	..	—	..
	72	—	—	—	..	..	..	—	..
17	24	—	—	—	..	+	..	—	..
	48	—	—	—	..	—	..	—	..
	72	—	—	—	..	—	..	—	..
18	24	—	—	+	..	—	..	+	..
	48	—	—	—	..	—	..	—	..
	72	—	—	—	..	—	..	—	..
19	24	—	—	—	..	—	..	—	..
	48	—	—	—	..	—	..	—	..
	72	—	—	—	..	—	..	—	..
20	24	+	—	—	..	+	..	—	..
	48	—	—	—	..	—	..	—	..
	72	—	—	—	..	—	..	—	..
21	24	+	—	—	..	+	..	..	..
	48	—	—	—	..	—	..	..	..
	72	—	—	—	..	—	..	..	..

* "P. V." indicates Sauer's pertussis vaccine (Eli Lilly & Co.), of which 0.1 cc. was given intradermally; U. B. A.," Kreuger's undenatured bacterial antigen, of which 0.1 cc. was given intradermally; "S.," 0.5 per cent phenolized saline solution, of which 0.1 cc. was given intradermally; used as a control for Sauer's vaccine.

TABLE 2.—*Results of Cutaneous Tests for Susceptibility to Whooping Cough: Group 2*—Continued*

Patient	Interval After Inoculation, Hr.	Tests Made Before Immunization			Tests Made After Immunization				
		P. V.	U. B. A.	S.	1 Mo. P. V.	2 Mo. P. V.	3 Mo. P. V.	4 Mo. P. V.	5 Mo. P. V.
22	24	+	+	—	..	+	..	..	..
	48	—	—	—	..	—	..	..	..
	72	—	—	—	..	—	..	..	..
23	24	+	+	—	..	..	+	..	..
	48	+	—	—	..	..	+	..	..
	72	+	—	—	..	..	—	..	..
24	24	+	—	+	+	..	+	..	..
	48	—	—	—	+	..	—	..	..
	72	—	—	—	+	..	—	..	..
25	24	—	—	—	+	..	—	..	..
	48	—	—	—	—	..	—	..	..
	72	—	—	—	—	..	—	..	.
26	24	—	—	—	+	..	—	..	..
	48	—	—	—	—	..	—	..	..
	72	—	—	—	—	..	—	..	..
27	24	+	—	—	..	..	+	..	..
	48	—	—	—	..	..	+	..	..
	72	—	—	—	..	..	—	..	..
28	24	+	—	—	..	—	..	..	..
	48	—	—	—	..	—	..	..	..
	72	—	—	—	..	—	..	..	..
29	24	—	—	—	+	..	..	..	..
	48	—	—	—	—	..	..	..	..
	72	—	—	—	—	..	..	..	..
30	24	+	—	—	+	..	..	..	..
	48	—	—	—	—	..	..	..	..
	72	—	—	—	—	..	..	..	..
31	24	+	+	+	+	..	..	..	..
	48	—	—	—	—	..	..	..	..
	72	—	—	—	—	..	..	..	..

The injections were made as in group 1 except that the readings were recorded at twenty-four, forty-eight and seventy-two hour intervals. The immunizations were carried out in the same manner, except that Lilly's preparation of the Sauer vaccine was used. Retesting was done as before.

RESULTS IN GROUP 2

The experiment was completed on 31 subjects.

After twenty-four hours 6 reactions to undenatured bacterial antigen and 3 reactions to phenolized saline solution were positive. These were negative after seventy-two hours. Before immunization, 17 of the reactions to pertussis vaccine were positive after twenty-four hours, but only 1 was positive after seventy-two hours. After immunization with a total of 41 tests done at various intervals with pertussis vaccine, only 8 reactions were negative after twenty-four hours, but all except 1 were negative after seventy-two hours.

COMMENT

While it is irrelevant to the original purpose of the paper, an interesting fact was noted. In group 1 (National Drug Vaccine Company), 26 were carefully followed for three years after immunization. There were 9 reported exposures to the disease; 6 of the exposed children contracted pertussis, and in 4 cases involvement was severe.

As for group 2 (Sauer's vaccine, Lilly), only eighteen months has elapsed since the last inoculation; 21 of the children have been followed, with 5 known exposures reported and no cases of whooping cough.

CONCLUSIONS

There is no evidence that intracutaneous testing as here described indicates whether a subject is susceptible or immune to whooping cough.

Results of the tests made after treatment with pertussis vaccine showed no routine correlation, and there was no specific variation from the reactions obtained before such treatment.

In the reactions observed in this experiment, there was nothing to suggest that a state of allergy developed after treatment with Sauer's vaccine.

As intradermal testing failed to give specific results, it cannot be considered of value in detecting susceptibility or immunity to whooping cough.

POSTMEASLES ENCEPHALITIS

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In 1933 we reported 13 cases of encephalitis complicating measles.[1] This was the largest single series of cases of this disease entity reported in the literature to that date. These cases occurred during an extensive epidemic of measles in 1931 and 1932 (15,001 cases reported). The monthly incidence of the complications was proportionate to that of measles. Milwaukee experienced another epidemic of measles in the first five months of 1938 (27,081 cases reported). During this period we observed, mainly through the permission of our colleagues, 14 cases of postmeasles encephalitis. We wish to report our findings in these cases. The essential clinical data are summarized in table 1. The laboratory findings are listed in table 2.

It may be noted that in our entire series of 27 cases the clinical and the laboratory findings present a clearcut picture, suggesting a definite disease entity. All of the patients except 1 were under 10 years of age. There was no apparent relation between the severity of the measles, the height of the fever or the extent of the rash and the appearance of encephalitis. The signs and symptoms of the complication were usually noted on or about the fourth day after the appearance of the rash. In the majority of cases the physical and the mental condition of the patient were considered to be normal before the onset of measles. The predominant picture was one of cerebral involvement: Eleven patients became stuporous or comatose, and 7 had convulsions. The usual neurologic symptoms were stupor or convulsions, rigidity of the neck and spasticity of the extremities. These findings varied from day to day. The rectal temperature usually ranged around 102 F.

Polymorphonuclear leukocytosis was noted in the majority of cases in which a blood count was made. The spinal fluid was usually under increased pressure and showed an increased cell count. Most of the cells were lymphocytes. The test for globulin usually gave a positive reaction, and the sugar content was normal or slightly increased. The colloidal gold curve usually showed a change in the middle, or meningitic, zone.

1. Peterman, M. G., and Fox, M. J.: Encephalitis as a Complication of Measles, Am. J. Dis. Child. **46**:512 (Sept.) 1933.

TABLE 1.—*Clinical Findings in Fourteen Cases of Postmeasles Encelphalitis*

Case No.	Patient	Sex	Age, Years	Time of Onset of Encephalitis, Number of Days After Rash Appeared	Time First Seen, Number of Days After Onset of Encephalitis	Rectal Temperature on Admission	Symptoms	Signs	Outcome
1	C. R.	M	32	4	1	100 (mouth)	Nausea, vomiting, convulsions, stupor	Slight rigidity of neck; reflexes accentuated; twitching of facial muscles; Kernig and Babinski signs absent; extremities spastic	Complete recovery
2	D. S.	F	6	5	Same day	102	Marked stupor; coma until death	Facial twitchings; nystagmus; slight rigidity of neck; marked flaccidity of all extremities; Kernig and Babinski signs absent; abdominal reflexes absent; paralysis of bladder	Died
3	S. DeN.	F	3	3	1	103	Irritability	Stiffness of neck; Kernig and Brudzinski signs present	Complete recovery in one month
4	W. A. C.	M	9	4	2	102	Drowsiness; cried when hurt by spinal tap	Pupils small and equal; rigidity of neck; Babinski and Brudzinski signs present	Complete recovery
5	A. T.	F	6	4	Same day	105	Sore throat, convulsions, coma, photophobia, epiphora	Spasmodic twitching of right side of face; horizontal nystagmus; flaccid paralysis of right arm and leg; Babinski sign present on left; loss of abdominal reflexes	Complete recovery
6	H. E.	M	6	3	Same day	102	Convulsions, coma, cyanosis, fatigue	No rigidity of neck; reflexes all normal; on fourth day had rigidity and paralysis of diaphragm on right	Complete recovery
7	T. F.	M	6½	3	2 (?)	102	Vomiting, drowsiness, convulsions, coma	Rigidity of neck; pupils dilated; reflexes hyperactive	Complete recovery
8	J. McF.	M	6	4	1	100	Clonic convulsion, somnolence, slow response to questioning	Slight rigidity of neck; reflexes not present; Brudzinski and Kernig signs present	Complete recovery
9	P. R.	F	7	5	3 hr.	101	Clonic convulsion, dyspnea, cyanosis	Carpopedal spasm; pupils dilated; neck rigid; Kernig and Brudzinski signs strongly present	Complete recovery
10	M. E.	M	8	4	....	101.8	Irritability, malaise, vomiting, headache, general discomfort	Abdominal reflexes gone; knee jerks absent; Babinski sign present; Kernig and Brudzinski signs absent	Complete recovery
11	B. S.	F	7	3	Same day	100	Semicoma, stupor	Rigidity of neck; hyperactive reflexes; photophobia	Complete recovery
12	G. D.	M	7	2	....	104	Drowsiness, lethargy	Rigidity of neck; generalized spasticity; bulbar paralysis developed	In coma at time of writing*
13	A. G.	F	11½	4	Same day	101.6	Headache, convulsions, coma changing to delirium	Rigidity of neck; tendon reflexes hyperactive	Complete recovery
14	L. S.	F	4	3	Same day	102	Drowsiness, coma	Slight rigidity of neck	Bulbar paralysis; died

alysis; died

TABLE 2.—*Laboratory Findings in Fourteen Cases of Postmeasles Encephalitis*

Case No.	Number of Leukocytes per Cu. Mm.	Neutrophils, Percentage	Number of Days After Onset	Spinal Fluid				
				Pressure	Number of Cells per Cu. Mm.	Globulin, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Colloidal Gold Reaction
1	6,850	84	5	Normal	250 98 lymphocytes 2 polymorphonuclears	Ross-Jones-Noguchi test, positive reaction	92	012332100
2	.....	..	6	Slightly increased	503 99 lymphocytes 1 polymorphonuclear	Increased	50	0123321000
3	2,800	82	6	Increased	160 67 lymphocytes 33 polymorphonuclears	Trace; Ross-Jones-Noguchi test, faintly positive reaction	..	0122210000
4	14,600	70	9	Increased	45	Positive reaction	80	
5	.....	..	9	Increased	77 96 lymphocytes 4 polymorphonuclears	.....	65	0122100000
6	40,900	72	4	.....	15	Ross-Jones-Noguchi test, positive reaction	93	0000000000
7	10,800	60	2	Increased	510, mostly lymphocytes	Increased	77	
8	.....	30	8	Slightly increased	68 17 polymorphonuclears 83 lymphocytes	Ross-Jones-Noguchi test, negative reaction	64	0000000000
9	26,300	67	7	.....	143 98 lymphocytes 2 polymorphonuclears	Ross-Jones-Noguchi test, faintly positive reaction	62	0122210000
10	.....	..	0	Increased	16 7 polymorphonuclears 93 lymphocytes	Slightly increased	44	
11	15,900	78	10	Increased	83 5 polymorphonuclears 95 lymphocytes	Slightly increased	70.5	
12	16,400	76	6	Increased	330 55 lymphocytes 45 polymorphonuclears	Increased	87	0123321000
13	11,000	47	4	Increased	150	Negative reaction	104	0122100000
14	19,800	..	4	Increased	80	Positive reaction	..	1233210000

Of the entire series of 27 patients, 8 died and 19 recovered, a mortality of 29.6 per cent. In 17 cases the recovery was complete, without residual abnormality. At the time of writing, 1 child of the first series (F. G.) is a helpless mental cripple, and 1 child of the last series (G. D.) is still in coma.[1a] The necropsy observations on 3 patients in our first series have been reported.

In our previous report we presented a review of the literature and a discussion of the pathologic changes in postmeasles encephalitis. Since then we have reviewed additional reports.[2] In 1928 Ford collected 113 cases from the literature and added 12 of his own.[3] Our observations were similar to his. Ten per cent of his patients died. Of those who survived, 65 per cent showed residual symptoms, such as ataxia (30 per cent), mental defect (12 per cent), personality changes (17 per cent) and "epilepsy" (5 per cent). Wohlwill examined the brain and spinal cord in 5 cases of measles and pneumonia.[4] In 2 no pathologic changes were noted. In 1 there was an unusually large number of glial rosettes in the white matter of the cord, with no relation to the blood vessels.

Greenfield summarized his histologic observations in a case of postmeasles encephalitis,[5] in which the main changes were (1) diffuse congestion of the brain, especially of the white matter, sometimes causing petechial hemorrhages; (2) discrete perivascular infiltration with round cells (often absent in such cases), and (3) small perivascular zones

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1a. Since completion of this article G. D. has died.

2. Barnes, G. A. E.; Blake, J. C.; Hograth, J. C., and Mitman, M.: Encephalitis in Measles: Report of Five Cases with One Death and One Recovery After Convalescent Measles-Encephalitis Serum, Lancet **1**:687 (March 20) 1937. Levaditi, C.; Nicolau, S., and Sanchis Bayarri, V.: L'étiologie de l'encéphalopathie post-vaccinale, Presse méd. **35**:161 (Feb. 5) 1927. Price, H. W.: Measles Encephalitis, Canad. M. A. J. **36**:43 (Jan.) 1937. Reimold, W.: Ueber encephalitische Syndrome im Verlaufe von Infektionskrankheiten, Monatschr. f. Kinderh. **37**:336, 1927. Stern, W.: Die epidemische Encephalitis, ed. 2, Berlin, Julius Springer, 1928. Zimmerman, H. M., and Yannet, H.: Encephalomyelitis Complicating Measles: Report of Case with Necropsy, Arch Neurol. & Psychiat. **24**: 1000 (Nov.) 1930. Zischinsky, H.: Zwei Fälle von Masern mit zerebralen Komplikationen, Jahrb. f. Kinderh. **144**:353 (June) 1935.

3. Ford, F. R.: Nervous Complications of Measles, Bull. Johns Hopkins Hosp. **43**:140 (Sept.) 1928.

4. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

5. Greenfield, J. G.: The Pathology of Measles Encephalomyelitis, Brain **52**:171 (July) 1929.

of demyelination. The latter is the most characteristic change in this form of encephalomyelitis.

Walthard reported a case of encephalomyelitis which developed during an acute stage of measles.[6] Death occurred after four and one-half weeks of illness. A histologic summary mentioned widespread perivascular glial formation with marked destruction of the myelin sheaths and axis-cylinders in the region of the centrum ovale and in the basal ganglions. In places there was extensive glial proliferation, and in certain parts of the cortex and in the anterior horn of the cord there was extremely slight perivascular round cell proliferation of isolated vessels.

Sulzer reported 3 cases of complications of the central nervous system after measles and 2 cases of postinfectious ataxia, in 1 of which the condition was probably also a sequela of measles.[7] The clinical picture and the pathologic changes corresponded to those described.

McCausland and McClendon reported a case in which encephalographic study was used to establish the diagnosis.[8] We have found no difficulty in making the diagnosis and would not use such a drastic procedure during an acute inflammatory disease of the brain.

Ford and Guild observed 3 cases of postmeasles encephalitis which was followed by precocious sexual development.[9]

Malamud reported 2 cases and concluded that the clinical course, the pleocytosis in the spinal fluid and the pathologic alterations proved that this acute inflammatory disease is a true encephalitis produced by the virus of measles.[10]

COMMENT

It is our opinion that postmeasles encephalitis, or encephalomyelitis complicating measles, is an entity as distinct as the encephalitis which

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6. Walthard, K. M.: Spätstadium von Masernenzephalitis: Bemerkungen zur Histologie und Pathogenese der Masernenzephalitis, Deutsche Ztschr. f. Nervenh. **111**:117, 1929; Spätstadium einer "Encephalitis" nach Masern: Bemerkungen zur Histologie und Pathogenese, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:176, 1930.

7. Sulzer, H.: Zur Frage der sogenannten Masernenzephalitis, Jahrb. f. Kinderh. **128**:394 (Aug.) 1930.

8. McCausland, A. M., and McClendon, S. J.: Encephalitis Following Measles: Case Report with Encephalogram, Arch. Pediat. **51**:178 (March) 1934.

9. Ford, F. R., and Guild, H.: Precocious Puberty Following Measles Encephalomyelitis and Epidemic Encephalitis, Bull. Johns Hopkins Hosp. **60**: 192 (March) 1937.

10. Malamud, N.: Encephalomyelitis Complicating Measles, Arch. Neurol. & Psychiat. **38**:1025 (Nov.) 1937.

follows vaccination against smallpox.[11] We believe that the disease is an acute inflammatory lesion of the brain caused by a neurotropic virus of measles which accumulates in the brains of certain patients. This entity, or complication, must be kept in mind by every physician who deals with measles. It can be easily recognized and usually occurs only during epidemics of measles. On or about the fourth day after the appearance of the rash the child suddenly becomes drowsy, lethargic or comatose, or a convulsion develops. Examination then reveals dilated pupils, exaggerated reflexes and usually some degree of cervical rigidity. The blood count as a rule shows polymorphonuclear leukocytosis. The spinal fluid reveals an increase of cells, usually of lymphocytes, an increase in globulin and a colloidal gold curve with the greatest change of color in the middle, or meningitic, zone (0123321000). The sugar content of the fluid is usually normal or elevated unless the blood sugar level is low. No further examinations are necessary or advisable to establish the diagnosis. There can be no misinterpretation of this clinical picture.

As for therapy, we are convinced that at present it is limited to good nursing care and symptomatic treatment. As with poliomyelitis and with all virus diseases, when the earliest symptoms are recognizable the virus has already completed an irreversible reaction with the nerve cells.[12] There is no specific treatment, and measles convalescent serum cannot possibly be of value. Blood transfusions are worthless unless the patient is suffering from lack of red blood cells. Great care must be exercised to avoid overloading the patients with useless serum, blood or other fluids. If the spinal fluid is under increased pressure, daily punctures may be made to drain off the excessive fluid. One should not attempt to rouse the patient from his coma, for such efforts are fruitless. If the intracranial pressure is increased, magnesium sulfate may be given by mouth or intramuscularly every six hours or less frequently until the pressure is kept normal. We have not found sucrose of value in our cases. When convulsions supervene, the same treat-

11. Glanzmann, E.: Die nervösen Komplikationen der Varizellen, Variola und Vakzine, Schweiz. med. Wchnschr. **57**:145 (Feb. 12) 1927. Gorter, E., and van Nederveen, H. J.: Smallpox Vaccination in the Netherlands, Nederl. tijdschr. v. geneesk. **2**:1746 (Oct. 22); 2026 (Nov. 12) 1927; abstracted, Zentralbl. f. d. ges. Hyg. **17**:63, 1928. Keller, W.: Ueber Erkrankungen des Zentralnervensystems im Anschluss an die Kuhpockenimpfung, Nervenarzt **1**:729 (Dec. 15) 1928. Pette, H.: Das Problem der postvakzinalen Enzephalitis: Eine experimentell-biologische Studie, München. med. Wchnschr. **75**:207 (Feb. 3) 1928. Pette, H.: Die Stellung der postvakzinalen Encephalitis in der Reihe infektiöser Erkrankungen des Zentralnervensystem, Centralbl. f. Bakt. (Abt. 1) **110**:134 (Jan.) 1929. Pondman, A.: Bacteriological Researches in Postvaccinal Encephalitis, Nederl. tijdschr. v. geneesk. **2**:2037 (Nov. 12) 1927.

12. Rivers, T. M.: Viruses, J. A. M. A. **92**:1147 (April 6) 1929.

ment may be used to accomplish the same end. Excessive cerebral agitation may be treated with sedatives. Bulbar paralysis is usually fatal and can be relieved only by reducing intracranial pressure, by tube feeding and, when necessary, by giving artificial respiration. The disease is self limited and will run its course regardless of treatment. Overtreatment introduces the danger of overloading the circulatory system, of waterlogging the lungs or of causing cerebral thrombosis.

The mortality in our entire series was 29.6 per cent. Our only suggestion for the reduction of this rate is the treatment just outlined.

PAPULONECROTIC TUBERCULOSIS IN CHILDREN

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Tuberculous infections of the skin have been divided into two categories as to their source. There are those of exogenous origin and those of endogenous or metastatic origin. Cutaneous tuberculosis of exogenous origin usually manifests itself as a single progressive lesion which spreads by continuity or contiguity of tissues. Once the type has become well established in the individual case it usually remains characteristic throughout its duration. Tuberculosis spreading hematogenously has been subdivided into two classes, the one spreading by tumor formation and the other exanthematous. The exanthematous subdivision comprises lichenoid tuberculosis, papulonecroctic tuberculosis and erythematous rosacea-like tuberculosis with lupoid characteristics.

In order to comprehend the nature and significance of metastatic tuberculosis it is necessary to review the evolutionary mechanism in experimental animals. The classic experiments of Lewandowsky [1] on hematogenous tuberculosis showed that when tubercle bacilli were injected into the arterial blood of the ventricle of a normal guinea pig certain definite events occurred. After a preliminary incubation period of several weeks small papules covered with a scale became evident. This process gained momentum, and soon the guinea pigs became covered with a diffuse, coalescing papulosquamous eruption. If tuberculous guinea pigs were subjected to superinfection in the same manner, the majority promptly died of anaphylactic shock. The survivors showed a different type of cutaneous eruption. After the first day there were local edema, erythema and follicular accentuation, followed in two days by desquamation. In two weeks there were yellowish transparent circumscribed papules with adherent crusts.

Histologic examination of the tissues of the animals during the initial infection showed no characteristic tuberculoid architecture. There were ill defined infiltrates of polymorphonuclear leukocytes, lymphocytes, epithelioid cells and some fixed connective tissue reaction. Giant cells were absent; acid-fast tubercle bacilli abounded in all directions. The tissues after superinfection had occurred were different. They were

From the Department of Dermatology, University of Maryland School of Medicine.

1. Lewandowsky, F.: Die Tuberkulose der Haut, Berlin, Julius Springer, 1916.

characterized by sharply marginated infiltrates showing a tuberculoid structure, with many giant cells and epithelioid cells. There was marked periarterial caseation necrosis. Acid-fast tubercle bacilli were rarely found. Lewandowsky concluded that the body responds with a nonspecific inflammatory reaction when the tubercle bacilli are multiplying without check, the tuberculoid structure and tubercles being produced as a result of the previously formed bacillary antibodies disintegrating the tubercle bacilli. Gougerot [2] summarized this prevalent conception. He stated that the tuberculid (exanthematous, endogenous cutaneous tuberculosis) is a defensive mechanism aimed at destroying the bacillary embolism in a sensitized, semi-immunized person and that the skin defends itself not only through mononuclear and occasional polynuclear phagocytosis but through the use of lipolytic enzymes. This phenomenon of local bacteriolysis is stimulated by the circulatory antibodies produced by the cutaneous foci. These dermoantibodies act locally at the site of production and diffuse throughout the body.

The exanthematous forms of tuberculosis have been considered as reinfections or superinfections occurring in a person who had already been primarily infected. The clinical forms have been thought to depend on the allergic state and the localization of the lesion. If the person is anergic, either primarily or owing to the neutralization of a previous allergic state, there develops miliary tuberculosis with easily demonstrable bacilli. In the terminal stages of internal tuberculosis with negative anergy, tuberculosis orificialis ulcerosa develops generally from autoinoculation with abundant tubercle bacilli evident. If the patient has internal tuberculosis with positive allergy, one of the tuberculids develops and no demonstrable tubercle bacilli appear. The factors controlling the clinical picture are: the immune allergic state (gaged by the tuberculin reaction), the localization of the lesions, the type and route of infection and the number and virulence of the infecting bacilli. These factors are dependent on each other, but the chief factor is the specific reaction of the patient, and that is changeable.

Recent investigators [3] have observed a life cycle of the tubercle bacillus and afforded an opportunity to reinterpret the traditional conception of cutaneous tuberculosis. This new factor may be finally

2. Gougerot, H., in Deliberationes Congressus dermatologorum internationalis, Leipzig, Johann Ambrosius Barth, 1935, vol. 1, pp. 372-383.

3. (*a*) Mellon, R. R., and Fisher, L. W.: Newer Studies on the Filtrability of Pure Cultures of the Tubercle Group of Micro-Organisms, J. Infect. Dis. **51**: 117, 1932. (*b*) Mellon, R. R.: The Newer Biology of the Tubercle Bacillus: Its Variability, Filtrability, and Life-Cycle Changes, in Goldberg, B.: Clinical Tuberculosis, Philadelphia, F. A. Davis Company, 1935, chap. 2. (*c*) Miller, F.: The Induced Development of Non-Acid-Fast Forms of Tubercle Bacillus and Other Mycobacteria, J. Exper. Med. **56**:411, 1932.

correlated to explain the previously mentioned variable factor, namely the immune allergic state. Mellon and Beinhauer [4] have shown that in certain types of cutaneous tuberculosis the patient is anergic to the conventional type of tuberculin but becomes allergic when tuberculin prepared from different stages of the life cycle of the bacillus is used. Future investigations may show that a person may present multiple allergic responses, depending on the stage of the life cycle and the source of the testing tuberculin. Mellon stated that the interplay between host and parasite results in the evolution of phases of the parasite that modify considerably the clinical course of the disease and its pathologic manifestations. If this is accepted, one may conclude that the type of cutaneous disease depends on the state of the tubercle bacillus at the time of formation of the embolism. Despite innumerable attempts, no unquestioned, classic, acid-fast tubercle bacilli have been found or cultured in cases of lichenoid or papulonecrotic tuberculosis. Modern investigators employing newer technics have failed. Van Krieken,[5] employing guinea pig inoculations and Löwenstein's culture medium, could not demonstrate tubercle bacilli. Schmidt [6] was unable to demonstrate tubercle bacilli by culture in 8 cases of papulonecrotic tuberculosis. The search has been for the classic acid-fast forms. Now that efforts are being made to culture the organism at different stages, positive results may be forthcoming. One of the chief difficulties is that at certain stages in its life cycle the organism becomes sterile.

In each of the following 5 cases of papulonecrotic tuberculosis the histologic picture was characteristic. Each patient presented evidence of having had internal tuberculosis (primary focus) for some time. Each patient gave a positive reaction to old tuberculin, designative of a marked degree of the immune allergic state. As a rule it may be stated that all patients with papulonecrotic tuberculosis show a marked reaction to tuberculin. This, however, must be interpreted not as a specific response to the cutaneous lesions but as an allergic reaction to the primary tuberculous focus elsewhere in the body. In the cases here reported routine acid-fast stains did not reveal the presence of the classic tubercle bacillus. In sections stained by Gram's method and examined under oil immersion many clumps of blue-staining coccoid or minute bacilli were present. That they were not contaminants was made manifest by the fact that

4. Beinhauer, L. G., and Mellon, R. R.: Pathogenesis of Noncaseating Epithelioid Tuberculosis of the Hypoderm and Lymph Glands, Arch. Dermat. & Syph. **37**:451 (March) 1938.

5. van Krieken, J. A.: Untersuchung nach dem Typus der Tuberkelbacillen bei auf Tuberkulose beruhenden Hauterkrankungen, im besonderen bei Lupus vulgaris, Arch. f. Dermat. u. Syph. **175**:662, 1937.

6. Schmidt, P. W.: Zur Frage der atypischen hämatogenen Hauttuberculosen, Arch. f. Dermat. u. Syph. **175**:539, 1937.

they were observed in the pathologic architecture, deeply situated and in various localities. Further, different sections in diverse cases were stained, and careful search always revealed these bacteria. In only the last few cases have cultural attempts been made. These will form the basis of a future report.

The histologic structure of all tuberculids appears variable, but certain features remain acceptable as criteria, although not categorically. In papulonecrotic tuberculosis the chief damage has been done to the blood vessels in the midcutis. There follows obliteration of the smaller arteries, endophlebitis, with thrombosis and recanalization of the lumens of the

Fig. 1.—Papulonecrotic tuberculosis. The section (× 66; hematoxylin and eosin stain) shows early necrosis of the epidermis with vacuolization and loss of staining properties. Note the infiltrate closely packed in the papillary layers of the cutis.

vessels. Before canalization becomes complete, necrotic crusted ulcers have developed. The infiltrate is usually characteristic, with tubercle formation and some caseation necrosis. In the lichenoid tuberculids the histologic picture shows an infiltrate around the hair follicles, around the sweat glands or independent of either. The hair follicles have a rich blood supply conveyed by smaller and finer arterioles. The infiltrate may consist of pure epithelioid tubercles, an occasional giant cell and a narrow zone of lymphocytes at the border.

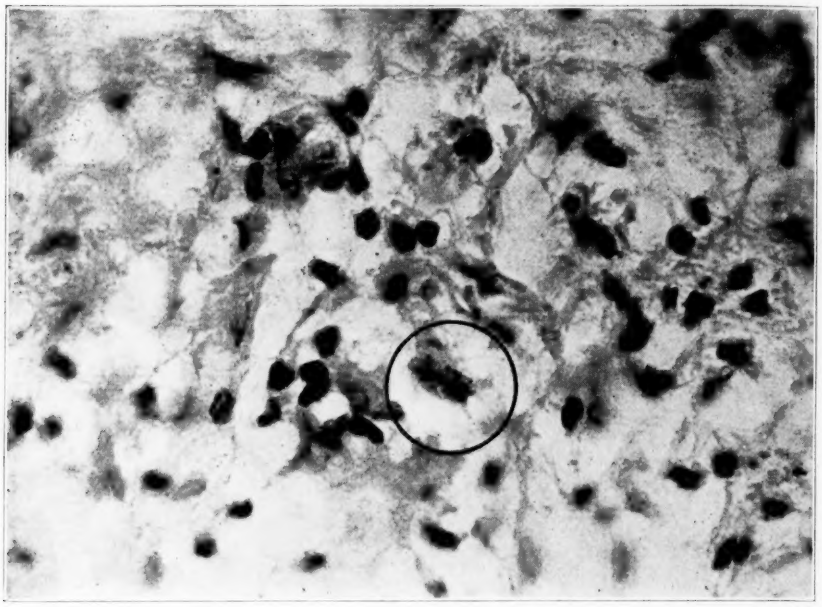

Fig. 2.—Papulonecrotic tuberculosis. The section (× 640; Gram's stain) shows coccoid or diphtheroid gram-positive bacteria deep in the infiltrate.

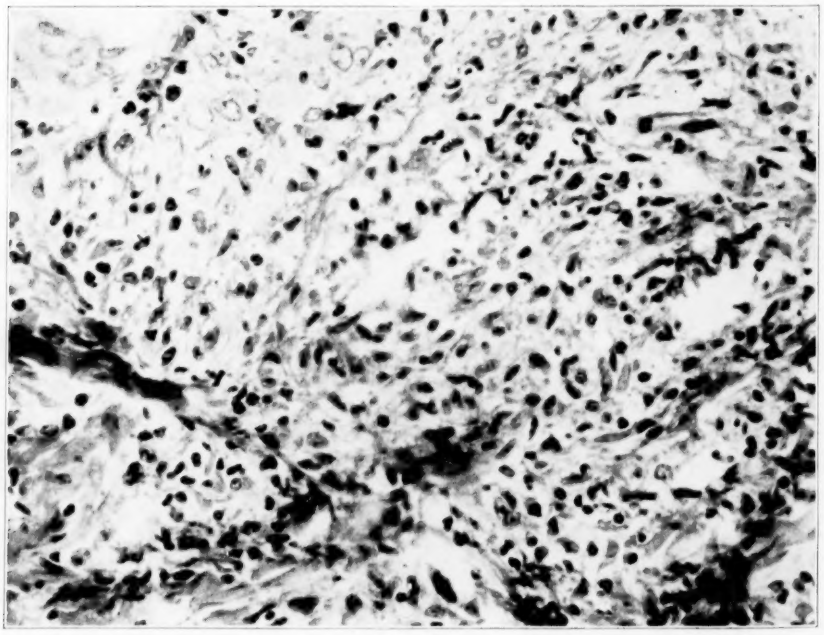

Fig. 3.—Papulonecrotic tuberculosis. The section (× 326; hematoxylin and eosin stain) shows the character of the cellular reaction.

REPORT OF CASES

CASE 1.—B. D. N., a boy aged 10 years, had a cutaneous eruption in January 1933. Although generalized, it was most prominent on the right upper portion of the torso and on the superior extremity. There were lesions over the right side of the body and numerous evenly distributed papules over the buttocks and lower extremities. The primary lesion was an acuminate, rounded papule about 1 to 3 mm. in diameter. Some of the lesions showed a central depression and scale. On the right side these papules formed irregular or linear patches covering an area about 5 cm. square. On the right arm there was a linear group of lesions extending laterally from the tip of the little finger to the elbow. To the right of the naval there was a patch extending to the pubis and sharply marginated. There were many scattered lesions over the legs and some hyperkeratosis over the elbows, knees and feet. The larger group of papules had acquired a hyperpigmented appearance. The papules on the lower extremities were larger and measured up to 6 mm.; they were not eroded or ulcerated. There were a few small pustules scattered over the face and back but none on the eyelids. The scalp was free of lesions. There was marked conjunctivitis of both eyes, with the usual accompanying symptoms. General glandular enlargement was absent. The accessible mucous membranes were free of lesions. The palms and soles were also free.

General physical examination revealed an impaired note over the apex of the right lung. Numerous sonorous rales were heard in the same region, and sibilant rales were evident over the entire chest.

Roentgen examination showed the heart to be of average size. The aorta was normal in width. There was a marked increase in the hilar shadows on the right side, with peribronchial infiltration in the upper lobe of the right lung. The changes were suggestive of mediastinal tuberculosis. Examination of the sputum did not reveal any acid-fast rods. The Kolmer test of the blood gave a negative reaction. Injection of tuberculin intradermally (0.001 mg.) produced a papule 20 by 25 mm.

Two biopsies were performed. Two fresh acuminate papules 1 mm. in diameter on the lower part of the right forearm were excised. This section showed papulonecrotic tuberculosis. Material for the second biopsy was taken from one of the patches of grouped, angulated papules on the right side. This section had the appearance of tuberculosis lichenoides.

CASE 2.—D. B. B., a boy aged 9 years, in 1930 complained of considerable pain in the right lower extremity, and shortly thereafter sinuses appeared above the right foot. A diagnosis of multiple tuberculosis of the bone was made, and the right leg was amputated. Later, draining sinuses developed on the right hand; this was followed by sinus formation over the left foot, with subsequent inguinal adenitis, ulceration and sloughing. The cutaneous lesions were principally on the lower portion of the trunk, the extremities, the left knee, the thighs and the forearms. There were many lesions, all papular. They presented no special grouping, although most of the lesions on the left lower extremity were grouped within an area of 12 cm. They varied in diameter from 1 to 4 mm. and in some areas were in the process of involuting. The smaller lesions were minute follicular papules, some of which were possessed of flat tops. The larger lesions became pustular and finally acquired depressed tops, with some crust formation. They appeared markedly inflammatory.

The Kolmer test of the blood gave a negative reaction. The tuberculin reaction was strongly positive (amount not stated).

The biopsy specimen showed papulonecrotic tuberculosis.

CASE 3.—J. W., a Negress aged 4 years, had had an aunt who died of tuberculosis at 16 years of age. The only child of this aunt had died of tuberculosis in infancy. J. W. had been exposed to the aunt and her child since birth. Because of these contacts the child was examined at 8 months of age, and a diagnosis of mediastinal tuberculosis was made. Roentgen examination at this time showed thickening of the mediastinal shadows on the left side, due to an enlarged gland.

Fig. 4 (case 3).—Papulonecrotic tuberculosis of the face.

The trachea was displaced to the right. Roentgen examination of the chest six months later showed a definite shadow in the left upper mediastinal region, which was due to enlarged glands. Comparison with the previous plate showed some increase in these shadows.

The patient had had an acute vesicular dermatitis about two years previously, which had involuted without sequelae. At present the cutaneous lesions were generally distributed over the scalp, face, eyelids, arms and legs and sparingly over the body. In the scalp there were many papules associated with the hair follicles, some of which were necrotic and purulent. On the face there were many small acuminate papules about 2 to 3 mm. in diameter, the apexes of which had become necrotic and purulent and in some instances been replaced by a yellowish gray crust. Some of these older papules had become yellowish red. These

were not eroded but in the process of involuting had assumed this color. The papules covered the entire face, including the eyelids and ears, but were most profuse in the flush area.

On the body were scattered papules (fig. 5), the majority of which were similar in color to those on the face. Over the lumbar region there were many

Fig. 5 (case 3).—Papulonecrotic tuberculosis of the lower extremities.

grouped shining follicular papules 0.5 to 1 mm. in diameter. In some localities they appeared as mere accentuated follicular markings (tuberculosis lichenoides).

The papules on the arms were similar to those on the face but were less profuse. On the legs the majority of the lesions were limited to the anterior surface. Here the papules were larger, measuring 4 to 5 mm. The centers were necrosed and crusted but not exudative. About the periphery of each lesion the epidermis had become scaly and showed a well defined halo. Where the lesions were involuting they appeared hyperpigmented.

There were marked conjunctivitis and iritis of both eyes, because of which they were kept closed continuously.

The Kolmer reaction of the blood was negative. The patient gave a marked intradermal reaction to 0.1 mg. of tuberculin.

Fig. 6 (case 5).—Nodose type of tuberculosis indurativa on the lower extremities.

Roentgen examination at the age of 4 years showed some decrease in the shadows as compared with the previous finding.

A biopsy was performed on material from the two lesions on the forearm. Microscopic examination revealed papulonecrotic tuberculosis.

CASE 4.—R. A., a Negress aged 7 years, had had a cutaneous disease for four months. There were lesions on the face, body and extremities. On the flush

area of the face, particularly the lips, nose and adjacent skin, there were many discrete papules from 1 to 2 mm. in diameter, brownish and acuminate, with a depressed central necrotic crusted area. On the anterior surface of the chest were many scattered similar papules. On the back there were innummerable papules in various stages of involution. Some were barely perceptible, others ranged up to 3 mm. in diameter. On each elbow the papules were 5 mm. in diameter, moderately indurated, hyperpigmented and possessed of large central crusted necrotic zones.

The cervical glands in the anterior triangle on the left were matted together, enlarged and intact.

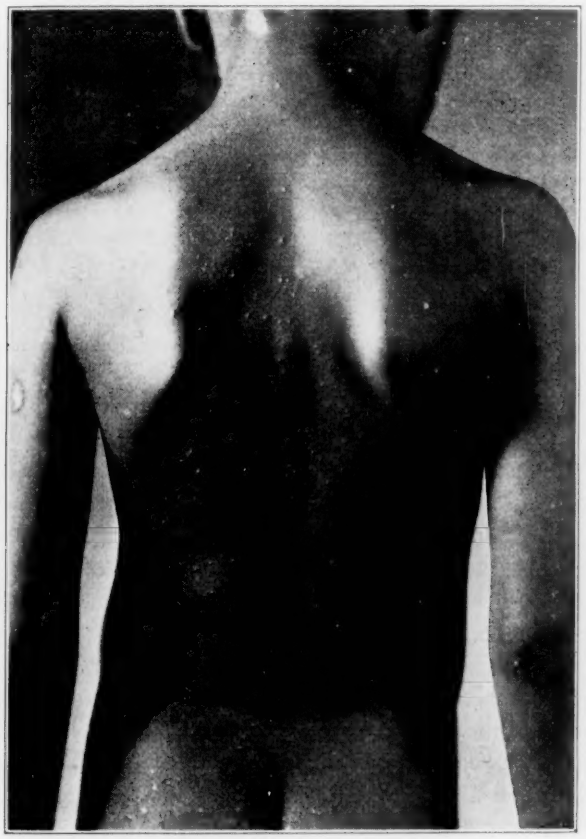

Fig. 7 (case 5).—Papulonecrotic tuberculosis of the back.

There had been a tuberculous ulcer of the left eye, which had involuted.

The Kolmer reaction of the blood was negative. The intradermal test with 0.1 mg. of tuberculin gave a marked reaction.

Physical examination of the chest gave negative results, but roentgen examination showed chronic mediastinal tuberculosis.

A biopsy was performed, and four small grouped papules were excised. Examination showed a follicular tubercle.

Cultural studies were incomplete but progressing.

CASE 5.—G. A., a Negress aged 5 years, had a gradually developing cutaneous disease present for two weeks. The lesions first appeared on the legs (fig. 6), and later the eruption was noted on the back (fig. 7). The lesions on the legs were present on all aspects. They were deeply seated erythematous nodules and tumors measuring about 6 to 8 mm. in diameter. The superficial skin was intact but tense. Most of the tumors were discrete, but where they were profuse many had coalesced into a confluent patch. Palpation was not painful. On the body the numerous papules were most prominent on the back. Here the papules were irregularly arranged, yellowish brown, acuminate, 0.5 to 3 mm. in diameter and possessed of a minute central depressed necrotic crust.

The tentative clinical diagnosis was papulonecrotic tuberculosis of the back and nodose type of erythema induratum of the lower extremities.

The Kline serodiagnostic test for syphilis gave a negative reaction. Examination of the chest revealed some evidence of mediastinal tuberculosis.

The reaction to 0.001 mg. of tuberculin resulted in marked inflammation, necrosis and sloughing.

Roentgen examination of the chest revealed changes consistent with the diagnosis of chronic mediastinal tuberculosis.

Two biopsies were performed. One of the small papules on the body showed the characteristic histologic structure of papulonecrotic tuberculosis. The second biopsy was performed on one of the nodules on the leg. The histologic picture here showed arterial thrombosis with periarterial caseation necrosis, numerous epithelioid cells and an occasional giant cell and lymphocyte. The infiltrate was sharply marginated and situated deep in the subcutaneous tissues. This architecture was consistent with the clinical diagnosis of the nodose type of erythema induratum.

COMMENT

The mechanism of cutaneous exanthematous tuberculosis, while not definite, depends on several fixed factors. The patient must have had some form of tuberculosis, so that the immune allergic state has developed. Then a dissemination of either the tubercle bacillus or some phase of its life cycle must occur. Whether this represents metastasis from the primary infection (Ghon's tubercle) or a superinfection or reinfection cannot be stated at this time. But whenever a patient presents exanthematous tuberculosis that patient must be considered as having definite internal tuberculosis, and the condition should be evaluated from that rather than from the cutaneous point of view. The prognosis for patients who have tuberculids is better than for those who do not. The cutaneous lesions usually involute without other sequelae.

The type of cutaneous lesions depends on the site of embolism. Careful search and care in selecting the site from which to take material for biopsy are necessary, and one can usually predict what the histologic picture will be. If when dissemination occurs the smaller and finer arterioles become involved, the patient will have lichenoid tuberculosis. This is due to the fact that the hair follicles and sweat glands have a rich anastomosis of arterioles. If the larger arterioles in the cutis become involved, papulonecrotic tuberculosis develops. After throm-

bosis ensues and before canalization or collateral circulation is established, the tissue supplied becomes necrotic and dead. After canalization and reestablishment of the blood supply, the lesions involute. When the site of thrombosis is in the larger arterioles or arteries deep in the cutis or in the fatty layer, erythema induratum develops. If many vessels become thrombosed and large areas of tissue are deprived of their blood supply, necrotic ulcers develop, and the question of healing depends on the amount of arterial damage. If many diffuse deep arteries become thrombosed, the nodose type of erythema induratum develops, and ulceration does not occur.

Thus the entire clinical picture depends on the amount of arterial damage, and while the various tuberculids have different gross morphologic descriptions they are merely variants of one another and are all produced by the essential factors as initially outlined. The difference between a lichenoid tuberculid, a papulonecrotic tuberculid and erythema induratum (tuberculosis indurativa) is merely a matter of relative tissue involvement, and one or all varieties may occur simultaneously in the patient.

In conclusion, these types of cutaneous tuberculosis assume great diagnostic and prognostic significance, and the ultimate outcome of the generalized tuberculosis depends not on the cutaneous disease but on the extent of visceral parenchymatous involvement. Since the presence of cutaneous lesions signifies a high degree of immunity, the immediate outlook becomes favorable. Later events will depend on the internal process and the treatment of the lesions.

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EVALUATION OF THE TUBERCULIN PATCH TEST (VOLLMER-LEDERLE)

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AND
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In 1937 we[1] described a patch test originated by one of us (Dr. Vollmer) in which old tuberculin of the New York Health Department was used. The test proved to be a simple, agreeable and harmless one with reliability approximating that of the Pirquet test. No disagreeable local reaction and no focal or general constitutional reactions were observed.

Since the publication mentioned, the reliability of the test has been improved by the use of a stronger tuberculin, and now, with two years of experience in the application of the test, we feel that a new evaluation of the method and a comparison of it with the standard method of tuberculin testing in the United States, the Mantoux method, are required. In the present paper we report our experience with 678 children.

METHOD

Thin filter paper is saturated with undiluted tuberculin produced from a synthetic medium (after Seibert[2]), dried, cut into squares 1 by 1 cm. and placed on adhesive tape 2.5 by 7.5 cm. Each strip of tape contains two such tuberculin patches placed at least 1 cm. apart, on each side of a control square which consists of a square of filter paper of equal size saturated with glycerin broth. The adhesive side is protected with crinolin, which has to be removed before the application of the patches.

A cutaneous area over the sternum, over the inner side of the forearm or along the upper portion of the spine (where the patches cannot be reached and removed by younger children) is cleansed with acetone, ether or purified petrolatum benzine. Cutaneous regions covered with hair should be avoided. The patch test is carefully applied to the cleansed area. After forty-eight hours the patches are removed. Bathing should be avoided while the patches are in place.

From the Pediatric Service of the Mount Sinai Hospital and the Sea View Hospital (chief of staff, Dr. Béla Schick).

1. Vollmer, H., and Goldberger, E. W.: New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019 (Nov.) 1937.

2. Seibert, F. B.: Isolation and Properties of Purified Protein Derivative of Tuberculin, Am. Rev. Tuberc. **30**:713 (Dec.) 1934.

The tuberculin used is not only four times stronger than the usual old tuberculin, but it is applied dry, i. e., in its most concentrated form. This tuberculin concentrate is liquefied by the natural moisture of the skin (insensible perspiration) and can then be absorbed by the skin. The time at which this absorption begins varies, depending on the individual degree of insensible perspiration as well as on the outside temperature; it takes place earlier in summer than in winter. The close contact between the skin and the tuberculin-saturated filter paper for forty-eight hours guarantees, even under unfavorable conditions (ichthyosis, myxedema, winter temperatures), a sufficient absorption of tuberculin to cause a cutaneous reaction.

The reaction may appear immediately after the removal of the patches. Since the cutaneous reaction is frequently delayed, it should be read forty-eight hours after removal of the adhesive tape. At this time the specific tuberculin reaction is more intensified, and any nonspecific cutaneous irritation caused by the adhesive tape will have subsided. In practice it may be convenient to let the mother or nurse remove the adhesive tape at the end of forty-eight hours and bring the patient to the physician's office forty-eight hours later for observation of the reaction.

Photograph showing a positive reaction to the patch test. *A* represents a 2 plus reaction; *B*, a 1 plus reaction. (This photograph is reproduced by courtesy of the Lederle Laboratories.)

As the accompanying illustration shows, a positive reaction appears as a sharply defined, indurated, reddened square with lichenoid follicular elevations. Quantitative degrees can be differentiated, if desired, as follows:

+	a few lichenoid efflorescences (*B*)
++	lichenoid-follicular eruptions assembled in a clearcut square (*A*)
+++	confluent eruption with marked induration and elevation in square form
++++	spread of the cutaneous reaction beyond the square area, and blister formation

Marked positive reactions usually cause itching, sometimes, in addition, burning, a sensation which subsides on the average after two days. The reaction remains visible for about a week and may result in scaling, discoloration or pigmentation discernible for several weeks. Lasting pigmentation or depigmentation, however, does not result even in Negroes.

In no instance was a focal or a general constitutional reaction observed after application of the tuberculin patch test in cases of either inactive or active tuberculosis. Even the simultaneous application of two or several patch tests did not cause the slightest elevation of body temperature.

VALUE OF THE TUBERCULIN PATCH TEST

A comparative study of the tuberculin patch test and the Mantoux test has been carried out on 678 children, who can be divided into two different groups.

GROUP 1.—Four hundred and seventeen children admitted to the Mount Sinai Hospital were tested with the Mantoux test (0.1 mg. of old tuberculin) and the tuberculin patch test simultaneously. The tests were carefully applied, and there were repeated opportunities of reading and following the reactions. Even unusually late reactions did not escape observation. The results are shown in table 1.

Of 417 children, only 4, or about 1 per cent, showed no conformity between the Mantoux test with 0.1 mg. of old tuberculin and the tuberculin patch test. Of these 4 children, 3 gave reactions favoring the tuberculin patch test. Consequently, the reliability of the patch test was practically 100 per cent.

TABLE 1.—*Comparative Results of Tests*

Cases	Mantoux Test with 0.1 Mg. O. T.	Tuberculin Patch Test
28	+	+
385	—	—
1	—	+
1	—	±
1	±	+
1	+	±
417		

GROUP 2.—Two hundred and sixty-one children in the Sea View Hospital, Staten Island, N. Y., with active tuberculosis were tested with the Mantoux and the tuberculin patch test. The intracutaneous test was carried out partly with 0.01 mg. of old tuberculin and partly with first strength solution of purified protein derivative. Only negative reactors to these solutions were retested after three days with stronger concentrations of tuberculin, old tuberculin in amounts up to 1 mg. or purified protein derivative in second strength solution. The patch test was repeated in only 6 cases. The tests were carried out under conditions similar to those of group 1. A higher sensitivity to tuberculin was expected. Table 2 shows the results.

Of 261 children with active tuberculosis, 259, or 99.23 per cent, showed conformity between the Mantoux and the tuberculin patch test. One child had a positive reaction to the patch test and a negative reaction to the Mantoux test with purified protein derivative in first strength solution. Only 1 child with positive anergy failed to react to the patch test as well as to the Mantoux test performed with first strength

purified protein derivative who reacted to the Mantoux test with second strength solution of purified protein derivative. Accordingly, the reliabilty of the tuberculin patch test as compared with the Mantoux test performed with second strength purified protein derivative amounts to 99.62 per cent, and to 100 per cent as compared with the Mantoux test performed with first strength purified protein derivative or with old tuberculin in amounts up to 1 mg.

COMMENT

The question to be answered by this comparative study of 678 children was whether or not the patch test can be safely substituted for the Mantoux test. It is not feasible to summarize the results in a percentage figure stating the degree of conformity or relative reli-

TABLE 2.—*Comparative Results of Tests in Group Two*

	Mantoux Test			Tuberculin Patch Test	
Cases	PPD I	PPD II	OT (0.01 mg.)	1	2
164	+	..	..	+	..
2	—	—	..	—	—
1	—	..	..	+	..
1	—	+	..	—	—
1	—	+	..	—	+
1	..	..	—	—	—
1	..	..	— (up to 1 mg.)	—	—
1	..	..	+	—	+
79	..	..	+	+	..
261					

In this table, PPD I indicates first strength purified protein derivative; PPD II, second strength purified protein derivative; OT, old tuberculin.

ability of the tests. Such a figure would be misleading for several reasons. In the first place, the Mantoux test, with which the patch test is to be compared, is not an infallible method; false positive reactions occur, particularly with the use of high concentrations of purified protein derivative. Technical errors, as well as disagreement in the interpretation of a cutaneous reaction, are encountered. Moreover, a certain percentage figure may have an entirely different meaning in different groups of children. One hundred per cent conformity in a group of children with active tuberculosis by no means proves the reliability of a test and can be reached even by a test of relatively low sensitivity. Therefore the good results obtained in the group of tuberculous children at the Sea View Hospital are no sufficient criterion. More significant are the results for the group in the Mount Sinai Hospital, where 417 unselected children admitted to the wards were tested routinely. None who showed a positive reaction to the Mantoux test

with 0.1 mg of old tuberculin failed to react simultaneously to the patch test. There were even more positive reactors to the patch test than to the Mantoux test.

Recently, Hart [3] in England reported on a series of 536 children in whom the Lederle tuberculin patch test and the Mantoux test with 0.1 mg. of old tuberculin or less produced identical reactions. This result corresponds with our findings.

It seems, therefore, that the Mantoux test with 0.1 mg. or less of old tuberculin or with first strength solution of purified protein derivative can be replaced by the tuberculin patch test, at least as the first test. Of course, higher concentrations of tuberculin must later be applied intracutaneously in order to rule out completely any tuberculous infection. It is a question whether the patch test is not preferable to the Mantoux test as the first diagnostic measure. Certainly, disagreeable local, focal and constitutional reactions occasionally result from the Mantoux test which have never been observed as a result of the patch test.

We therefore suggest the following routine for tuberculin testing: 1. The tuberculin patch test (Lederle) is applied and read two days after removal of the patches. 2. Negative reactors to the patch test are retested with the Mantoux test with 1 mg. (0.1 cc. of solution 1 : 100) of old tuberculin or second strength solution (0.005 mg.) of purified protein derivative. 3. Since higher concentrations of tuberculin occasionally cause pseudopositive reactions, both tests are repeated if there is any discrepancy. If the discrepancy remains, the Mantoux reaction is regarded as the deciding one.

This procedure is advocated for exact diagnosis in hospital wards. For general use in practice and for mass examinations the tuberculin patch test alone may suffice.

SUMMARY

A comparative study of the tuberculin patch test (Lederle-Vollmer) and the Mantoux test has been carried out on 678 children.

Among 417 children admitted to the wards of the Mount Sinai Hospital, the reliability of the tuberculin patch test as compared with the Mantoux test performed with 0.1 mg. of old tuberculin was 100 per cent.

Two hundred and sixty-one tuberculous children of the Sea View Hospital showed 100 per cent conformity between the tuberculin patch test and the Mantoux test with first strength solution of purified protein derivative or 0.01 to 1 mg. of old tuberculin. Only 1 child with positive anergy failed to react to the patch test as well as to the Mantoux

3. Hart, F. D.: Lancet **2**:609 (Sept. 10) 1938.

test with first strength purified protein derivative. This child reacted positively to the Mantoux test with second strength purified protein derivative.

Consequently it seems that the Mantoux test with 0.1 mg. of old tuberculin or less or with first strength solution of purified protein derivative can safely be replaced by the tuberculin patch test.

A routine is suggested for tuberculin testing, the tuberculin patch test being proposed as the first test.

25 Central Park West.

BLOOD CALCIUM AND PHOSPHORUS IN THE NEWBORN

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Most investigations on the calcium and phosphorus content of the blood of newborn infants have been approached through studies of rickets and tetany. The results of such investigations revealed that the figures for total serum calcium are below the accepted normal standard in tetany but remain unchanged in rickets. These same studies have helped to establish normal values of calcium and phosphorus for the infant and to develop technics for the determination of these constituents. Many papers dealing with this subject have substantiated the findings of previous authors that the newborn child has 1 to 2 mg. more calcium per hundred cubic centimeters of serum than does the adult; this is particularly noticed in the relative values for mother and child immediately after parturition.

The work presented in this paper was undertaken as part of a general study dealing with the nutritional status, particularly in relation to rickets, of preschool children and newborn infants in Portland, Ore. The results of the general study will be published in papers by Dr. C. Ulysses Moore and his associates. The present paper deals with calcium and phosphorus values for normal newborn babies with no attempt to correlate clinical and laboratory data.

A summary of data taken from the available literature dealing with blood calcium and phosphorus of the newborn is presented in table 1. Of the twenty-two authors listed in this table, only eight directed their work toward phosphorus. There are included a total of 832 cases in which the calcium content was determined and a total of 645 in which the phosphorus content was determined. The Kramer-Tisdall method for calcium was used in the majority of instances, although some of the recent investigators employed the Clark-Collip modification. No significant geographic variations are indicated in this table. The determina-

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From the Department of Biochemistry, University of Oregon Medical School, and the Multnomah County Hospital (Dr. Chuinard).

Authors	Calcium			Phosphorus			Source	Where Done	Year	Method
	No. of Cases†	Average	Range	No. of Cases	Average	Range				
Aburel, E., and Ornstein, I.: Compt. rend. Soc. de biol. **104**: 1247-1249 (Sept. 20) 1930	20	10.6	8.3-13.2	...	....	.....	Cord	Paris	1930	Grigaut-Ornstein (Grigaut, A., and Ornstein, J.: Compt. rend. Soc. de biol. **104**: 747-749 (June 21) 1930)
Aburel, E., and Ornstein-Cernantianu, E.: Compt. rend. Soc. de biol. **105**: 286-287 (Nov. 4) 1930	6	11.2	9.5-14.4	...	....	.....	Cord	Paris	1930	Delaville
McKellips, C. M.; DeYoung, I. M., and Bloor, W. R.: J. Biol. Chem. **47**: 53-58 (June) 1921	..	....	.....	7	9.7	7.7-11.3	Fontanel	Berkeley, Calif.	1921	Not given
Howland, J., and Marriott, W. McK.: Quart. J. Med. **11**: 289-319 (July) 1918	4	10.9	10.7-11.3	...	....	.....	Cord	Baltimore	1917	Marriott-Howland
Howland, J., and Kramer, B.: Am. J. Dis. Child. **22**: 105-120 (Aug.) 1921	7	10.8	10.4-11.3	...	....	.....	Cord	Baltimore	1921	Kramer-Tisdall
Riesenfeld, Handelmann and Rose [4]	..	....	.....	535	4.1	1.9- 7.2	Cord	New York	1925	Tisdall
Howland, J., and Marriott, W. McK.: Tr. Am. Pediat. Soc. **28**: 202-209, 1916	3	10.8	10.7-11.0	...	....	.....	Cord	New York	1916	Marriott-Howland
Bakwin and Bakwin [3]	300	11.0	8.5-13.5	...	....	.....	Cord	New York	1932	Kramer-Tisdall
Bogert, L. J., and Plass, E. D.: J. Biol. Chem. **56**: 297-307 (June) 1923	23	10.9	.....	...	....	.....	Cord	Detroit	1923	Kramer-Tisdall
Jones [6]	68	12.3	12.0-12.5	...	....	.....	Fontanel	San Francisco	1921	Lyman
Andersch, M., and Oberst, F. W.: J. Clin. Investigation **15**: 131-133 (Jan.) 1936	25	11.8	10.9-12.6	...	....	.....	Cord	Iowa City	1936	Kramer-Tisdall
Hess and Matzner [9]	21	10.75	9.1-11.0	21	3.71	2.9-4.41	Cord	New York	1923	Calcium: Lyman Phosphorus: Bell and Doisy
Ray and Phatak [7]	18	11.3	9.9-12.4	18	4.94	4.4- 5.6	Fontanel	San Francisco	1930	Kramer-Tisdall
Bloxsom, A., and Nicholas, H. O.: South. M. J. **26**: 883-887 (Oct.) 1933	1	11.2	.....	1	7.2	.....	External jugular vein	Houston, Tex.	1933	Phosphorus: not given Calcium: Kramer-Tisdall
Nicholas, H. O.; Johnson, H. W., and Johnston, R. A.: Am. J. Obst. & Gynec. **27**: 504-510 (April) 1934	8	12.2	11.0-13.6	8	7.2	4.4-13.3	Cord	Houston, Tex.	1934	Calcium: Clark-Collip Phosphorus: Fiske-Subbarow
Mull, J. W., and Bill, A. H.: Am. J. Obst. & Gynec. **23**: 807-814 (June) 1932	36	11.7	10.2-13.1	34	5.8	3.8- 6.1	Cord	Cleveland	1932	Calcium: Kramer-Tisdall Phosphorus: not given
György, P.: Jahrb. f. Kinderh. **102**: 145-172 (June) 1923	23	11.0	.....	21	5.4	.....	Cord	Heidelberg, Germany	1923	Kramer Tisdall
Nohlen, A.: Ztschr. f. Kinderh. **42**: 60-65, 1926....	19	12.7	.....	...	....	.....	Cord	Düsseldorf, Germany	1926	Calcium: de Waard
Bokelmann, O., and Bock, A.: Arch. f. Gynäk. **133**: 308-330, 1928	16	10.5	9.71-12.64	...	....	.....	Cord	Berlin	1928	Kramer-Tisdall
Bokelmann, O., and Bock, A.: Arch. f. Gynäk. **133**: 739-746, 1928	19	11.07	9.31-12.64	...	....	.....	Cord	Berlin	1928	Kramer-Tisdall
Timpe, O., and Hellmuth, K.: Arch. f. Gynäk. **145**: 411-422, 1931	186	9.9	7.8-12.7	...	....	.....	Cord	Berlin	1931	Kramer-Tisdall
Hellmuth, K.: Klin. Wchnschr. **4**: 454-455 (March 5) 1925	29	11.8	10.0-13.8	...	....	.....	Cord	Berlin	1925	Clark
Recapitulation‡	745	10.85	8.3-14.4	619	4.26	1.9-13.3	Cord			
	87	12.08	9.9-12.5	26	6.31	4.4-11.3	Fontanel			
Total	832	10.97	8.3-14.4	645	4.30	1.9-13.3	Both			
Todd, Chuinard and Wood										
Blood I	630	9.93	7.2-12.3	548	6.08	3.7- 8.6	Fontanel	Portland, Ore.	1935	Calcium: Clark-Collip
Blood II	573	10.45	7.5-13.9	530	5.93	3.5- 7.6	Fontanel	Portland, Ore.	1935	Phosphorus: Fiske-Subbarow
	121	11.27	7.3-16.9	121	5.55	4.2- 8.0	Cord	Portland, Ore.	1935	

* Values indicate milligrams per hundred cubic centimeters.

† In some of the papers regarding fontanel blood more cases were reported than are listed here, but we included only the cases of infants 10 days old or under, in order to make better comparison with our cases.

‡ In the recapitulation the data on fontanel and on cord blood were separated for better comparison with our results.

tions of calcium show an average of 10.97 mg. per hundred cubic centimeters, with a range of 8.3 to 14.4 mg. The determinations of phosphorus give an average of 4.3 mg. per hundred cubic centimeters, with a range of 1.9 to 13.3 mg.

PROCEDURE

For one year, from March 1, 1935, to March 1, 1936, all babies born at the Multnomah County Hospital who were found on routine physical examination to be in the usual state of health were subjected to two fontanel punctures. The first specimen of blood was taken on or before the third day of life (blood I), and the second specimen was taken during the period from the fourth to the seventh day inclusive (blood II). From 12 to 15 cc. of blood was removed at each puncture. This large quantity was necessary because of the unusually high cell volume in most cases.

The baby was placed on its back; the arms were wrapped snugly to the body, and the legs together, and the head was held firmly presented to the physician. A 22 gage needle 1 cm. in length was inserted into the superior longitudinal sinus at the posterior angle of the anterior fontanel, and the desired amount of blood was withdrawn and transferred to a test tube to clot.

The two samples of blood were taken at intervals to ascertain whether there is a tendency of the calcium value for the infant soon after birth to approach the lower value for the adult, as claimed by some investigators.

Within one to two hours after being drawn the blood was centrifuged, and a portion of the serum was precipitated for determination of the phosphorus content. Determinations of the calcium content were made by the Clark-Collip [1] modification of the Kramer-Tisdall method, and the phosphorus content was estimated by the Fiske-Subbarow method.[2] When not enough serum was obtained to permit determinations of both calcium and phosphorus, the former only was made.

RESULTS AND COMMENT

Calcium.—A summary of findings obtained by determinations of calcium in 639 cases during the period from March 1, 1935, to March 1, 1936, is presented in table 2. In this study the serum calcium level averaged 10.15 mg. per hundred cubic centimeters, with a range of 7.2 to 13.9 mg. The averages are grouped according to sex and seasons. It will be noted that there existed a slight, but definitely increased, value for calcium during the autumn and winter. This fact, verified by a statistical treatment of these data with a technic using the sigma of the difference, held for both blood I and blood II. It was due possibly to the prolonged effect of the summer's sun, with increased mobilization of calcium in the blood stream, or possibly to the maternal consumption of more fresh vegetables during the spring and summer, with resulting higher calcium values in the succeeding seasons. However, both these suggestions may be questioned in view of the fact that

1. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461-464 (March) 1925.

2. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375-400 (Dec.) 1925.

TABLE 2.—Calcium and Phosphorus Values of the Blood Serum of Newborn Infants

Calcium-Phosphorus

Phosphorus

Calcium

TABLE 2.—*Calcium and Phosphorus Values of the Blood Serum of Newborn Infants*

		Calcium, Mg. per 100 Cc.			Phosphorus, Mg. per 100 Cc.			Calcium-Phosphorus Product		
		Boys	Girls	Both	Boys	Girls	Both	Boys	Girls	Both
Blood I (Taken During the First Three Days of Life)										
March 1 to June 1, 1935 (Spring)	No. of cases	102	77	179	88	64	152	88	64	152
	Range	7.2-12.2	7.2-10.9	7.2-12.2	3.7-8.0	4.6-8.2	3.7-8.2	37.00-73.90	40.40-82.80	37.00-82.80
	Average	9.4	9.26	9.34	6.1	6.4	6.18	57.29	57.96	57.63
June 1 to Sept. 1, 1935 (Summer)	No. of cases	106	80	186	91	69	160	91	67	158
	Range	8.5-11.9	8.2-11.5	8.2-11.9	4.4-7.5	4.3-7.1	4.3-7.5	40.40-81.60	41.70-75.90	40.40-81.60
	Average	9.74	9.97	9.83	6.15	6.00	6.08	59.94	59.66	59.77
Sept. 1 to Dec. 1, 1935 (Autumn)	No. of cases	74	63	137	68	59	127	65	56	121
	Range	8.8-12.2	9.2-11.8	8.8-12.2	4.4-7.6	4.2-8.6	4.4-8.6	44.9-86.5	43.4-79.2	44.9-86.5
	Average	10.39	10.37	10.32	6.05	6.21	6.12	61.96	64.07	63.15
Dec. 1, 1935, to March 1, 1936 (Winter)	No. of cases	71	58	129	59	50	109	59	50	109
	Range	8.6-12.3	8.0-11.8	8.0-12.3	4.3-8.0	5.0-7.5	4.3-8.0	42.50-93.60	46.90-80.20	42.50-93.60
	Average	10.06	10.26	10.15	6.11	6.19	6.15	62.38	63.45	62.92
Average for the year	No. of cases	353	278	631	306	242	548	303	237	540
	Range	7.2-12.3	7.2-11.8	7.2-12.3	3.7-8.0	5.3-8.6	3.7-8.6	37.0-93.6	40.4-82.8	37.0-93.6
	Average	9.87	9.95	9.93	6.10	6.2	6.08	60.51	61.15	60.80
Blood II (Taken During the Fourth to Seventh Day of Life)										
March 1 to June 1, 1935 (Spring)	No. of cases	94	69	163	84	66	150	82	66	148
	Range	7.5-12.0	8.1-13.7	7.5-13.7	3.8-7.6	3.9-7.5	3.8-7.6	37.6-82.9	39.0-98.6	37.6-98.6
	Average	9.84	9.87	9.86	5.85	6.31	6.05	58.19	61.03	59.40
June 1 to Sept. 1, 1935 (Summer)	No. of cases	90	72	162	81	68	149	80	68	148
	Range	9.2-11.8	8.6-13.9	8.6-13.9	4.3-7.5	4.6-7.5	4.3-7.5	45.5-77.8	43.0-104.2	43.0-104.2
	Average	10.19	10.36	10.27	5.9	5.83	5.88	60.19	60.99	60.56
Sept. 1 to Dec. 1, 1935 (Autumn)	No. of cases	70	64	134	69	59	128	65	58	123
	Range	9.7-12.4	9.0-12.4	9.0-12.4	3.5-7.3	4.4-7.5	3.5-7.5	55.0-79.6	45.0-80.0	45.0-80.0
	Average	10.9	11.09	10.99	5.83	5.93	5.88	64.20	65.44	64.66
Dec. 1, 1935, to March 1, 1936 (Winter)	No. of cases	60	52	112	55	48	103	55	48	103
	Range	7.6-12.3	8.7-12.3	7.6-12.3	4.5-7.1	4.0-7.2	4.0-7.2	34.2-85.2	42.0-84.0	34.2 85.2
	Average	10.77	10.75	10.77	5.91	5.88	5.90	63.32	63.19	63.27
Average for the year	No. of cases	314	257	571	289	241	530	282	240	522
	Range	7.5-12.3	8.1-13.9	7.5-13.9	3.5-7.6	3.9-7.5	3.5-7.6	34.2-89.2	39.0-104.2	34.2-104.2
	Average	10.40	10.52	10.45	5.87	5.99	5.93	61.28	62.58	61.88
Average of Blood I and Blood II *										
March 1 to June 1, 1935 (Spring)	No. of cases	93	69	162	75	57	132	74	57	131
	Range	7.2-12.2	7.2-13.7	7.2-13.7	3.7-8.5	3.9-8.2	3.7-8.5	37.0-89.2	43.0-98.6	37.0-98.6
	Average	9.62	9.58	9.61	6.00	6.22	6.10	57.6	59.4	58.4
June 1 to Sept. 1, 1935 (Summer)	No. of cases	90	70	160	70	58	128	69	57	126
	Range	8.5-11.8	8.3-13.9	8.3-13.9	4.3-8.5	4.3-7.5	4.3-8.5	40.4-81.6	41.7-104.2	40.4-104.2
	Average	9.95	10.16	10.05	6.00	5.98	5.99	59.8	60.8	60.3
Sept. 1 to Dec. 1, 1935 (Autumn)	No. of cases	67	61	128	61	52	113	55	49	104
	Range	8.8-12.4	9.0-12.4	8.8-12.4	4.4-7.6	4.4-8.0	4.4-8.0	36.4-86.5	45.0-79.8	36.4-86.5
	Average	10.67	10.70	10.68	5.95	6.05	5.99	62.9	64.3	63.5
Dec. 1, 1935, to March 1, 1936 (Winter)	No. of cases	60	51	111	49	42	91	49	42	91
	Range	7.6-12.5	8.0-12.3	7.6-12.5	4.3-8.0	4.0-8.0	4.0-8.0	34.2-93.6	42.0-84.8	34.2-93.6
	Average	10.47	10.50	10.48	6.03	6.03	6.02	62.9	63.2	63.1
Average for the year	No. of cases	310	251	561	255	209	464	247	205	452
	Range	7.2-12.5	7.2-13.9	7.2-13.9	3.7-8.5	3.9-8.2	3.7-8.5	34.2-93.6	41.7-104.2	34.2-104.2
	Average	10.11	10.17	10.15	5.99	6.08	6.03	60.5	61.8	61.0

* This section of the table is comprised of data for cases in which figures were available for calcium and/or phosphorus in both blood I and blood II.

during the last two months of pregnancy a mother does not show the same response to sunshine or consumption of vegetables but has a calcium level 1 to 2 mg. lower.

Table 2 shows also a remarkable similarity in blood calcium values for boys and for girls. The correlation coefficient for serum calcium between blood I and blood II was 0.7, indicating a strong tendency for a high or low serum calcium level in blood I to remain relatively the same in blood II. However, values for serum calcium in blood II were significantly higher than those in blood I.

A disparity in the number of cases in the various sections of this table is due to the fact that under the column head "Average of Blood I and Blood II" only cases could be included in which determinations of calcium and/or of phosphorus for both classes of bloods were available. In a number of instances determinations were not made because of insufficient quantity of blood, loss of sample or other reasons.

The possible effects of the age and parity of the mother and of the weight of the child were studied. The age of the mother and the weight of the child were without influence on the values for either calcium or phosphorus. Infants born of mothers who had had three or more children, however, showed a slight, but significantly lower, serum calcium value.

Bakwin and Bakwin,[3] in a study of serum calcium in newborn infants and their mothers, found little or no correlation between the calcium level and such factors as season, age and sex of the baby or age and race of the mother. Their study was conducted during March, April, May, June, October and November.

Phosphorus.—Table 2 also summarizes our phosphorus values. The average for 639 cases was 6.03 mg. per hundred cubic centimeters. Seasonal variations in the blood phosphorus level were small, but were shown by statistical treatment to be significantly higher in the spring. This was true for both blood I and blood II. The sex and weight of the infant and the age and parity of the mother were not demonstrated to have any influence on the values.

It is interesting to note that Riesenfeld, Handelmann and Rose[4] found a seasonal variation of phosphorus values in their study of newborn infants. The values were lower in the spring (3.8 mg. per hundred cubic centimeters) and higher in the winter (4.5 mg.). They expressed the belief that humidity played a greater role than did sunlight. The inference was that humidity (moisture, precipitation) intensified the effect of the ultraviolet rays.

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3. Bakwin, H., and Bakwin, R.: Factors Influencing the Calcium Concentration in the Serum of New-Borns, Am. J. Hyg. **15**:766-772 (May) 1932.

4. Riesenfeld, E. A.; Handelmann, I, and Rose, A. R.: Inorganic Phosphorus in the Blood of the Newborn, Am. J. Dis. Child. **30**:646-658 (Nov.) 1925.

There is considerable difference between the average value of serum phosphorus obtained by us (6.03 mg.) and the general average (4.3 mg.) obtained by the investigators listed in table 1. This factor will be discussed under the heading "Comparison of Values for Cord and for Fontanel Blood."

Calcium-Phosphorus Product.—This was computed in all cases in which both the calcium and the phosphorus value had been determined. The calcium-phosphorus product is considered important by many investigators, who hold that a figure less than 40 is suggestive of rickets.

As the seasonal variations in the serum phosphorus level were slight, the calcium-phosphorus product showed the same seasonal variation as the serum calcium value. The average product for the year was 61.

Comparison of Values for Cord and for Fontanel Blood.—The use of fontanel blood offers several advantages over that of cord blood. Several specimens can be obtained and analyzed in the laboratory at one time. Furthermore, it can be arranged to secure these specimens when it is convenient for both the hospital and the laboratory. It is important to have the blood fresh in the daytime, as determinations of the phosphorus content must be made promptly. The comparative studies of cord and fontanel values may indicate that the fontanel method is more reliable for a clinical estimate; this will be discussed more fully later.

It may be recorded incidentally that in this series of 1,200 fontanel punctures and in another series of 200 made for determination of normal hematologic values [5] no immediate ill effects resulted to the baby, and no complaint traceable to the puncture has come to us. Many of these infants have been returning to the University of Oregon pediatric clinic and welfare clinics during the past two years for routine care, and no signs or symptoms referable to the fontanel punctures have been found.

Calcium: In 639 cases the serum calcium value averaged 10.15 mg. per hundred cubic centimeters, which is 0.82 mg. less than the average calculated from the data in table 1, which represent 832 determinations by other investigators. The difference in these values for calcium suggested to us the most apparent variable, namely, the source of the blood. It is seen in table 1 that Jones [6] and Ray and Phatak [7] obtained high values, 12.3 mg. and 11.3 mg. per hundred cubic centimeters, respectively, with blood obtained from the fontanel. To make possible a more

5. Chuinard, E. G., and Osgood, E. E.: Normal Hematology of the Newborn, to be published.

6. Jones, M.: The Calcium Content of Blood Plasma and Corpuscles in the New-Born, J. Biol. Chem. **49**:187-192 (Nov.) 1921.

7. Ray, H. H., and Phatak, N. M.: Diffusible Blood Serum Calcium in Normal Newborn Infants, Am. J. Dis. Child. **40**:549-556 (Sept.) 1930.

accurate comparison of our values for fontanel blood with other values in table 1, we separated the total and the average figures for cord and for fontanel blood in this table; they appear in the recapitulation.

In order to obtain a further comparison of the calcium and phosphorus values for cord and for fontanel blood, determinations were carried out on cord blood serum from infants who were later to be subjected to fontanel puncture. The worth of these results was enhanced by the fact that the determinations were carried out simultaneously by the same persons, who employed the same technic and methods. The average values for 65 such infants are listed in table 3. This table shows the average calcium value of the cord blood to be 10.98 mg. and of the fontanel blood (average of blood I and blood II) to be 9.62 mg. per

TABLE 3.—*Comparison of the Calcium and Phosphorus Contents of Cord and of Fontanel Blood Serum of 65 Newborn Infants*

	Range	Average
Cord blood		
Calcium	7.3-16.9	10.98
Phosphorus	4.2- 8.0	5.54
Calcium × phosphorus	39.9-83.2	61.75
Fontanel blood		
Blood I		
Calcium	7.7-11.1	9.33
Phosphorus	4.4- 8.0	6.2
Calcium × phosphorus	40.4-77.6	56.9
Blood II		
Calcium	7.5-11.7	9.96
Phosphorus	4.0- 7.1	5.74
Calcium × phosphorus	39.0-74.5	57.0
Average, blood I and blood II		
Calcium	8.2-11.4	9.62
Phosphorus	4.7- 7.3	5.97
Calcium × phosphorus	42.3-74.5	57.0

hundred cubic centimeters. The cord blood therefore had a higher calcium average than the fontanel blood. Our average calcium value for cord blood (10.98 mg.) corresponds closely with that of other workers (10.85 mg.). The value 9.62 mg. for fontanel serum calcium is decidedly lower than our yearly average. We believe that this is due to the fact that in this small series approximately 90 per cent of the tests were made in the two periods from March 1 to September 1, in which occurred the lowest seasonal average for serum calcium; furthermore, approximately 60 per cent of all these tests were made within the period from March 1 to June 1, the season in which the average calcium content was lowest. It is interesting further to note in this table that as the serum calcium value of blood II increased over that of blood I, the inorganic phosphorus content decreased, so that the calcium-phosphorus product remained virtually constant.

Our series of tests on cord blood actually included a total of 121 determinations, of which only 65 could be used in the comparison with values for fontanel blood. The remainder of these tests on cord blood

were made subsequent to the study on fontanel blood in order that the yearly average might be completed. It was possible to perform calcium and phosphorus tests only for infants born during the hours at which technicians were available. The yearly averages were 11.27 mg. of calcium per hundred cubic centimeters of serum and 5.55 mg. of inorganic phosphorus, with ranges of 7.3 to 16.9 mg. and 4.2 to 8.0 mg., respectively. The discrepancy between these figures and the averages in table 3, which cover 65 cases, has adequately been explained.

This presents an opportunity for speculation: Does the method of taking blood from the cord at a time when the physiologic condition of mother and child is undergoing so much change give a true indication of the condition of the newborn in regard to blood calcium? Many hematologists do not believe it is good technic to "milk" the finger or ear before or after puncturing it for hematologic examination. It seems to us that it is likewise impossible for all specimens obtained from the cord to be well mixed and free from variations in concentration and viscosity.

It has been shown by several investigators that the alterations in calcium values of the mother and child incident to birth soon readjust themselves. If we are to assume that our values for calcium content obtained with cord bloods are representative, we then must suppose that rapid readjustment occurs in the newborn infant almost immediately after birth. Many of the specimens constituting blood I were taken during the first day of life and thus more nearly approximated cord blood than samples taken later; yet such early samples did not raise the average values over those of the later specimens (blood II).

Phosphorus: Most authors have agreed that the phosphorus level in the serum of a newborn infant is 1 to 3 mg. per hundred cubic centimeters higher than in the adult. Osgood [8] gave the normal phosphorus value of an adult as 3 to 4 mg. and that of an infant as 4 to 6 mg.

The average of 619 determinations of the phosphorus content (of cord blood) by other investigators, as shown in table 1, is 4.26 mg. per hundred cubic centimeters. The largest group in this series consisted of the 535 cases reported by Riesenfeld, Handelmann and Rose,[4] in which the serum phosphorus averaged 4.1 mg. The average of 65 determinations on cord blood made by us was 5.54 mg., while of the 1,078 estimations of fontanel blood phosphorus, representing 639 cases, the average was 6.03 mg. This indicates that fontanel blood contains more phosphorus than does cord blood. The number of cases reported by Riesenfeld, Handelmann and Rose in regard to cord blood and by us in regard

8. Osgood, E. E.: Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co., 1935, p. 97.

to fontanel blood is so large that the averages are representative for the methods employed. Hess and Matzner [9] offered a suggestive explanation for this increase in phosphorus value; they pointed out that the excretion of phosphorus in the fetus is extremely slight and cited Heubner,[10] who stated that the amniotic fluid and the urine voided by the infant during the first eight hours of life contain only traces of phosphorus.

Changes in Calcium and Phosphorus: After a careful study of the material presented in this comparative study of values for calcium and phosphorus in fontanel and in cord blood, certain facts are apparent, and others may be inferred. There is an actual difference in the calcium and phosphorus values of cord and of fontanel blood. Calcium and phosphorus rapidly adjust themselves to a new equilibrium within twenty-four hours after birth. The level of serum calcium in our series changed from a value of 10.98 mg. for cord blood to one of 9.62 mg. for the corresponding fontanel blood, and the phosphorus level changed from a value of 5.54 mg. for cord blood to one of 5.97 mg. for fontanel blood (table 3). Thus, the changes in calcium and in phosphorus occur in opposite directions. Determinations on cord blood do not provide a true indication of the calcium and phosphorus values of the circulating blood of the newborn infant and are thus not conclusive for reliable clinical work. This statement may not hold for fontanel blood drawn two, six or ten hours after birth, as there is no information regarding the early postpartum hours. A study tracing the rapid adjustment that takes place in the first twenty-four hours would be interesting.

SUMMARY

A study has been made of the calcium and phosphorus in the serum of normal newborn infants delivered at the Multnomah County Hospital during one year. Blood was taken from the anterior fontanel, and in every case two samples were analyzed. The first (blood I) was withdrawn during the first three days of life, and the second (blood II) was taken during the period from the fourth to the seventh day. A total of 639 cases (1,202 calcium and 1,078 phosphorus determinations) are reported. The serum calcium value averaged 10.15 ± 0.022 mg. per hundred cubic centimeters, with a range of 7.2 to 13.9 mg. The inorganic phosphorus content averaged 6.03 ± 0.021 mg., with a range of 3.5 to 8.6 mg. The calcium-phosphorus product averaged 61. These figures are averages for blood I and blood II.

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9. Hess, A. F., and Matzner, M. J.: Rickets in Relation to the Inorganic Phosphate and Calcium in Maternal and Fetal Blood, Am. J. Dis. Child. **26**:285-289 (Sept.) 1923.

10. Heubner, W.: Phosphorus Excretion in the Newborn, Arch. f. exper. Path. u. Pharmakol. **62**:253-257, 1910.

A definite seasonal variation in the serum calcium level was found, with higher values in autumn and winter. The serum phosphorus value was slightly, but significantly, higher in spring. No variations in either element were referable to the weight or sex of the newborn infants. Babies of mothers who had three or more children showed significantly lower serum calcium levels. Blood II was significantly higher in calcium and lower in phosphorus than blood I. The calcium-phosphorus product followed the seasonal variations in serum calcium.

In 65 of these cases estimations on cord blood were made for comparison with the values of venous (fontanel) blood. In this series the calcium and phosphorus values of the fontanel blood (average of blood I and blood II) were 9.62 and 5.97 mg. per hundred cubic centimeters, respectively, while the corresponding values for the cord blood were 10.98 and 5.54 mg. The calcium-phosphorus products for cord and for fontanel blood were 61.75 and 57 mg., respectively.

An actual difference exists in the amounts of calcium and phosphorus contained in cord and in fontanel blood serum. Calcium was found to be lower and phosphorus higher in fontanel blood than in cord blood. The quantity of these elements is adjusted, however, to a new equilibrium within the first twenty-four hours of life. On this basis, determinations on cord blood do not provide a true indication of the calcium and the phosphorus content of the circulating blood of the newborn infant.

Dr. Harry R. Cliff, director of Multnomah County Hospital, cooperated in making this study possible.

Marian M. Wood and Fritzi G. Chuinard gave assistance in computation and statistical treatment.

CUTANEOUS REACTIONS TO TOBACCO ANTIGEN IN ALLERGIC AND IN NONALLERGIC CHILDREN

WITH DIRECT AND INDIRECT (LOCAL PASSIVE TRANSFER) METHODS OF TESTING

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Tobacco sensitization has become a subject of increasing interest, owing largely to the investigations conducted by Harkavy and his co-workers. The first reports [1] dealt with the occurrence of positive intracutaneous reactions to various tobacco antigens in 103 patients suffering from thromboangiitis obliterans (Buerger's disease). Sulzberger [2] confirmed these findings in a total of 24 cases of a similar condition. Harkavy [1] was the first to demonstrate successfully the existence of passive transfer reactions (Prausnitz-Küstner method) to tobacco. Later, with Witebsky,[3] he showed that sensitization of the normal skin on passive transfer with serums obtained from tobacco-sensitive patients could be inhibited by the previous absorption of the tobacco antibody in vitro. Quantitative titration of the tobacco antibody (reagin) in his patients disclosed a high degree of sensitivity to the tobacco extract employed. Quantitative titration of the antibodies for

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From the Children's Allergy Clinic and the Pediatric Service, Mount Sinai Hospital, New York.

1. Harkavy, J.; Hebald, S., and Silbert, S.: Tobacco Sensitiveness in Thromboangiitis Obliterans, Proc. Soc. Exper. Biol. & Med. **30**:104 (Oct.) 1932. Harkavy, J.: Tobacco Sensitiveness in Thromboangiitis Obliterans, Migrating Phlebitis and Coronary Artery Disease, Bull. New York Acad. Med. **9**:318 (May) 1933.

2. Sulzberger, M. B.: Studies in Tobacco Hypersensitivity: Comparison Between Reactions to Nicotine and to Denicotinized Tobacco Extract, J. Immunol. **24**:85 (Jan.) 1933; Addendum, ibid. **24**:265 (March) 1933. Sulzberger, M. B., and Feit, E.: Studies in Tobacco Hypersensitivity: Thromboangiitis Obliterans with Positive Urticarial Skin Reactions and Negative Reagin Findings, ibid. **24**: 425 (May) 1933.

3. Harkavy, J., and Witebsky, E.: Studies of Specificity in Multiple Hypersensitiveness by Quantitative Titration and Absorption of Reagins, J. Allergy **6**:437 (July) 1935.

timothy and for tobacco was also made. Preliminary addition of timothy extract to serum in vitro absorbs the reagin for timothy but not that for tobacco, and vice versa. In this manner they demonstrated that the antibody for tobacco and that for timothy are specific and independent. The evidence that tobacco protein is a true allergen was further adduced by Harkavy [4] in experimental work, in which he successfully sensitized male rats and was able to demonstrate anaphylactic reactions as well as the phenomenon of desensitization of the excised intestinal strip (according to the Schultz technic).

Trasoff, Blumstein and Marks,[5] in a study of 31 patients with thromboangiitis obliterans and 41 allergic patients, all adults, accounted for the increased incidence of cutaneous reactions to tobacco in the allergic patients on the ground that many nonspecific reactions are frequently obtained in such persons. These authors further contended that the failure to demonstrate reagins for tobacco on passive transfer in all patients except 1 also argued against the allergenic significance of this substance.

Chobot [6] tested 53 children with allergy with one tobacco extract (Virginia, 0.1 mg. of nitrogen per cubic centimeter) and found only 6, or 11 per cent, who gave completely negative reactions. He failed to demonstrate reagins on passive transfer in the serums obtained from 4 selected positively reacting patients. He concluded that tobacco must be regarded in the same light as morphine and histamine as an irritant which cannot be considered of clinical importance.

In view of the varied opinions concerning the interpretation of the cutaneous reactions to tobacco in normal and in allergic adults and in adults with organic disease as well as in children with allergy, it was felt that a detailed study of tobacco reactions in allergic and in nonallergic children who had not yet used tobacco in any form was warranted and would help to clarify and correlate the divergent opinions expressed in previous publications.

Our purpose in this paper was therefore to determine (1) the incidence of positive intradermal reactions to tobacco in the nonallergic child, (2) the reactions to tobacco by direct and indirect (local passive transfer) methods of testing in the allergic child, (3) the relation between tobacco and ragweed pollens as well as grass pollens and (4) the criteria of positive cutaneous reactions to tobacco.

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4. Harkavy, J.: Tobacco Sensitization in Rats, Proc. Soc. Exper. Biol. & Med. **36**:381 (April) 1937.

5. Trasoff, A.; Blumstein, G., and Marks, M.: The Immunologic Aspect of Tobacco in Thromboangiitis Obliterans and Coronary Artery Disease, J. Allergy **7**:250 (March) 1935.

6. Chobot, R.: The Significance of the Tobacco Reactions in Allergic Children, J. Allergy **6**:383 (May) 1935.

MATERIALS AND METHODS

This study is based on 200 afebrile nonallergic children and 164 allergic children, 86 of whom had pollen sensitization, 72 asthma without pollen allergy and the remainder urticaria, migraine and vasomotor rhinitis. The ages ranged from 2 to 15 years. Fifty children and 6 adults were selected for passive transfer. Sixty-seven adults (parents of the allergic children) with no personal histories of allergy were also studied.

The tobacco employed in this investigation consisted of the cured leaf of the Burley, Maryland, Virginia and Xanthis (Turkish) varieties. Separate extracts of these were prepared according to the method of Coca. The tobacco was first extracted with a mixture of alcohol and ether. The residue was later extracted with the Coca solution and was then dialyzed against buffered saline solution (for approximately three to four weeks) until the dialysate was free from coloring matter. Thin cellophane bags were used. The extracts were standardized by the nitrogen method, and each was employed in its original concentration (varying from 0.07 to 0.1 mg. of nitrogen per cubic centimeter).

The pollen extracts were prepared after the method of Coca. The maximum concentration was a 1:50 dilution, which was freshly prepared at least every two months. The ragweed extract consisted of equal parts of short and of giant ragweed. The grass extract contained equal parts of timothy, redtop and orchard and June grass.

The normal children were tested intradermally with various extracts of tobacco and with concentrated dialyzed extracts of mattress dust and ragweed and grass pollens. The adults were similarly tested, the dust extract being omitted. The pollen extracts were first employed in a 1:1,000 dilution (0.01 mg. of nitrogen per cubic centimeter); since no patient showed more than a 1 plus reaction, the test with the 1:50 dilution was next performed. Some of the patients who had had negative and plus-minus reactions with the weaker dilution of pollen extract had 1 to 3 plus reactions when the stronger dilutions were employed. Thus, the tables for the control group represent tests with a 1:50 dilution of pollens. In the selection of controls, children with a personal history, as well as those with a family history of allergy, were excluded.

The allergic children were routinely tested by the scratch method with the dry powdered extracts for sensitivity to food, pollens and inhalant substances, including tobacco. Dry powdered natural pollens were used. Pollens of short and giant ragweed, timothy, redtop, orchard and June grass, plantain and trees were employed for testing as a routine. When reactions to the scratch test were negative, the intradermal tests with the 1:50 dilution of extracts were next performed. In order to simplify the reading of the tables, a positive scratch reaction to pollen was recorded as a 3 plus intradermal reaction. The other reactions recorded in the tables represent tests with the 1:50 dilution of pollen. In other words, all the pollen reactions recorded in the tables are presented in terms of a 1:50 dilution. Plus-minus reactions with pollen, although recorded in all the tables, were interpreted by us as negative because we have found repeatedly that patients with such reactions (with the 1:50 dilution of pollen) showed no correlation between the reactions and the clinical symptoms.

The indirect method of testing was employed to determine the qualitative presence of reagins (antibodies) to the four tobaccos and to ragweed and grass pollen. The parents (mostly mothers) of the children were selected as recipients for passive transfer when they gave no personal history of allergy and reacted negatively when tested intradermally with the tobaccos and pollens in concentrated

solutions. Each parent accepted for transfer was first proved to be a receptor. Into the outer upper aspect of the arm, at a number of sites, was injected 0.1 cc. of undiluted serum to be tested. One to two days later these sites were tested with all of the antigens studied. Each passive transfer test was usually carried out on one normal receptor. All reactions greater than the reactions to the control test were regarded as positive.

When reactions (intradermal, direct method) to various substances are recorded, there seems to be a lack of agreement as to the significance of a plus-minus and of a plus reaction and in some instances even of a 2 plus reaction with respect to certain antigens as compared with others. When there is an apparent lack of correlation between presenting symptoms and positive cutaneous reactions to individual antigens, some authors have designated such results (regardless of the substance tested) as "false positive" or as negative, and in publication they have interpreted rather than recorded specifically the actual reactions. In dealing with tobacco, workers whose experience with this substance is limited would naturally misinterpret such reactions and probably record them as negative. Harkavy, however, in the light of our study, has justifiably read as positive all reactions to tobacco greater than the reaction to the control test. He employed readings ranging from plus-minus to 4 plus. This may be confusing to other investigators when they compare their findings, read according to accepted practice. In order to avoid any confusion, we have recorded all the intradermal reactions according to the original method as described by Cooke.[7] The details of the technic of the tests and the types of reactions were described by one of us (M. M. P.) and Fineman.[8] All reactions ranging from negative to 3 plus which were obtained by the direct and indirect methods of testing are recorded in the tables. It should be noted in this respect that the interpretation as to which reactions are to be recognized as positive rests not with the method of testing but with the test material employed.[8]

The tobacco extracts were injected intradermally because even in concentrated form they are relatively weak antigens. The difficulty of obtaining an appreciable number of positive reactions by scratch testing with concentrated solutions or with dry powdered extracts parallels the experience with dust extract.

THE NONALLERGIC CHILD

Cutaneous reactions in the normal child have not yet been studied. This is surprising in view of the volume of work already done on normal adult smokers and nonsmokers. We were therefore obliged to resort to the figures for adults as criteria in our studies.

Harkavy and Romanoff [9] and Harkavy [10] studied 200 adult smokers and 126 nonsmoking women. For the purpose of comparison with

7. Cooke, R. A.: Cutaneous Reactions in Human Hypersensitiveness, Proc. New York Path. Soc. **21**:8 (Jan.-May) 1921.

8. Peshkin, M. M., and Fineman, A. H.: Asthma in Children: A Comparative Study of the Scratch and Intradermal Methods of Skin Testing, Am. J. Dis. Child. **34**:815 (Nov.) 1927.

9. Harkavy, J., and Romanoff, A. J.: Skin Reactions to Tobacco and Other Allergens in Normal Men and Women Smokers, J. Allergy **6**:62 (Nov.) 1934.

10. Harkavy, J.: Skin Reactions to Tobacco Antigen in Smokers and Nonsmokers, J. Allergy **5**:131 (Jan.) 1934.

our series of nonallergic children, 59 of the 200 adult smokers who gave personal and family histories of allergy were excluded. Of the remaining 141 persons, 40, or 28 per cent, showed positive reactions to tobacco. Of the 126 women, the majority of whom were relatively recent immigrants and were ignorant of their family and personal histories of allergy, only 2 stated that they had a history of allergy. Among the remaining 124 women, the incidence of positive reactions to tobacco was 11 per cent.

Sulzberger [11] tested with tobacco 95 adult smokers in a hospital population with various diseases and 50 healthy adult smokers and found that 36 per cent had positive reactions. These figures cannot be used for comparison with those of our controls because of incomplete information with regard to family and personal histories of allergy. There was no difference between men and women in the percentage of positive reactions. Of 58 nonsmokers, 9, or 16 per cent, had positive reactions of the skin to tobacco.

Trasoff and his associates [5] tested 52 normal nonsmokers, of whom 11, or 21 per cent, showed slightly positive reactions to tobacco. Of 40 normal smokers 7, or 17 per cent, showed positive reactions.

Sixty-seven parents (58 women and 9 men) of the allergic children in our study were tested by us with all the tobaccos and pollens. None of these parents had a personal history of allergy so far as could be determined. Forty-four showed completely negative reactions to tobacco and pollens. Three had negative reactions to tobacco but positive reactions to pollens. The remaining 20 persons (30 per cent) showed positive reactions to tobacco. Of these, 5 were smokers, and 12 reacted to pollens. Positive reactions to pollen, as we shall show, are closely bound up with positive reactions to tobacco.

A. Cutaneous Reactions to Tobacco.—Table 1 shows the number and incidence of cutaneous reactions, ranging from negative to 3 plus, to Burley, Maryland, Virginia and Xanthis tobacco in 200 nonallergic children.

Table 1 shows that Virginia tobacco was only slightly less potent than the other tobaccos employed. Owing to the relatively small number of patients showing positive reactions to tobacco, the lower incidence of positive reactions to Virginia tobacco is not readily appreciated until table 3 is analyzed.

B. Age and Sex Incidence.—Figure 1 shows the comparative incidence of positive reactions to tobacco and pollen in the 200 nonallergic children (113 boys and 87 girls) with relation to age and sex.

The incidence of positive reactions to tobacco in boys and in girls was 19 and 16 per cent, respectively, while the corresponding incidence

11. Sulzberger, M. B.: Recent Immunologic Experiments in Tobacco Hypersensitivity, Bull. New York Acad. Med. **9**:294 (May) 1933.

of positive reactions to pollens was 19 and 18 per cent, respectively, the figures indicating no difference between the sexes.

With reference to age, it appears that the bulk of positive reactions to tobacco indicated in the curves for boys and girls and the corresponding positive reactions to pollen lay in the age period ranging from 4 to 9 years, with the peak at 6 to 7 years. There were so few subjects in the groups from 2 to 3 and 14 to 15 years of age that the curves for this category of patients should be discarded as not representative.

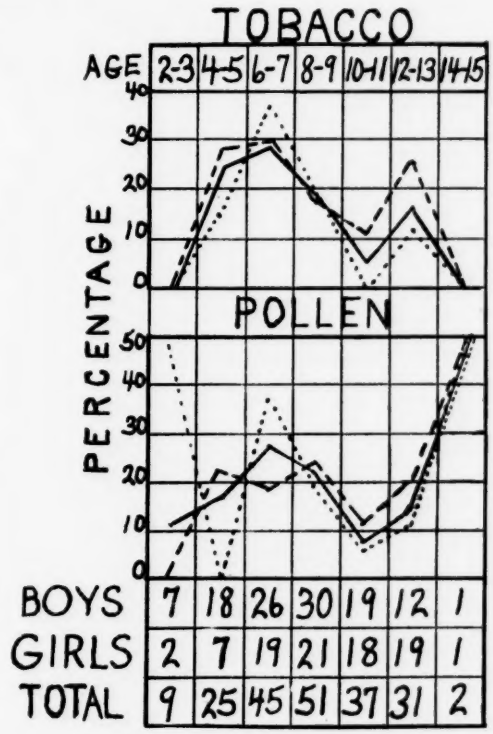

Fig. 1.—Comparative incidence of positive reactions obtained with tobacco and with pollen extract in 200 nonallergic children with relation to age and sex. In this figure and in figure 2 the solid line indicates both boys and girls; the line of dashes, boys, and the dotted line, girls.

C. Incidence of Comparative Reactions to Tobacco and to Pollen.—The next point under investigation was the incidence of reactions to tobacco and to pollen in 200 nonallergic children (table 2).

It may be noted in table 2 that the tobacco reactions which ranged from 1 to 3 plus comprised those of 13 per cent of the 200 nonallergic children and that the corresponding positive pollen reactions (1 to 3

plus) occurred in 85 per cent of this group. The plus-minus reactors to tobacco comprised 4.5 per cent of these children, and the incidence of corresponding positive reactions was 78 per cent. In other words, the percentage of positive pollen reactions in the children who showed 1 to 3 plus and the percentage in those who had plus-minus reactions to tobacco was almost the same, being 85 and 78 per cent, respectively.

TABLE 1.—*Incidence of Intracutaneous Reactions to Burley, Maryland, Virginia and Xanthis Tobaccos in 200 Nonallergic Children*

	Number of Reactions				Percentage of Reactions			
Cutaneous Reactions	Burley	Maryland	Virginia	Xanthis	Burley	Maryland	Virginia	Xanthis
1 plus	17	19	14	21	8.5	9.5	7.0	10.5
2 plus	1	1	2	3	0.5	0.5	1.0	1.5
3 plus	1	1	0	0	0.5	0.5	0.0	0.0
1-3 plus	19	21	16	24	9.5	10.5	8.0	12.0
Plus-minus	11	10	12	10	5.5	5.0	6.0	5.0
Total positive	30	31	28	34	15.0	15.5	14.0	17.0
Negative	170	169	172	166	85.0	84.5	86.0	83.0
Total	200	200	200	200	100.0	100.0	100.0	100.0

TABLE 2.—*Comparative Incidence of Intracutaneous Reactions to Tobacco and to Pollen in 200 Nonallergic Children*

			Pollen†									
			Number of Reactions					Percentage of Reactions				
	Tobacco* Reactions		Negative		Positive			Negative		Positive			Total
Cutaneous Reactions	No.	%	—	±	+	++	+++	—	±	+	++	+++	Positive
1 plus	23	11.5	1	2	13	6	1	4.4	8.6	56.5	26.1	4.4	87.0
2 plus	2	1.0	0	0	1	1	0	0.0	0.0	50.0	50.0	0.0	100.0
3 plus	1	0.5	1	0	0	0	0	100.0	0.0	0.0	0.0	0.0	0.0
1-3 plus	26	13.0	2	2	14	7	1	7.7	7.7	53.8	26.9	3.9	84.6
Plus-minus	9	4.5	2	0	6	0	1	22.2	0.0	66.7	0.0	11.1	77.8
Total positive	35	17.5	4	2	20	7	2	11.4	5.7	57.2	20.0	5.7	82.9
Negative	165	82.5	153	3	6	2	1	92.7	1.8	3.7	1.2	0.6	5.5
Total	200	100.0	157	5	26	9	3	78.5	2.5	13.0	4.5	1.5	19.0

* Only the largest reaction of the four tobaccos employed is recorded.
† Only the largest reaction of either ragweed or grass pollen is recorded.

The total incidence of positive reactions to tobacco (plus-minus to 3 plus) was 17.5 per cent, and the corresponding incidence of positive reactions to pollen was 83 per cent. In the group of 165 children with totally negative reactions to tobacco the incidence of positive reactions to pollen was 5.5 per cent.

The distribution of cutaneous reactions (not recorded in table 2) to pollen (ragweed, grass or both) in relation to the reactions to tobacco was as follows: Seventeen children showed positive pollen reactions to

ragweed alone. Thirteen of these, or 76 per cent, showed positive reactions to tobacco. Three children showed positive reactions to grass pollen alone. Two, or 67 per cent, gave positive reactions to tobacco. Eighteen children showed positive reactions to ragweed and grass pollens. Fourteen of these, or 78 per cent, reacted positively to tobacco. One hundred and sixty-two children showed negative reactions to pollen. Of the latter, 6, or 4 per cent, showed positive reactions to tobacco.

From the foregoing data, it can be stated that the incidence of positive reactions to tobacco in the children used as controls was approximately the same as the incidence of positive reactions to ragweed or grasses or to ragweed and grasses. Of a total of 38 children with positive reactions to pollen, 29, or 76 per cent, showed positive reactions to tobacco, as compared with 4 per cent of 162 children with negative reactions to pollen and positive reactions to tobacco. These findings were further corroborated by the comparable figures computed for the allergic children.

D. Relation Between Cutaneous Reactions to Dust and to Tobacco.—One hundred and fifty children of this nonallergic control group were tested with potent dialyzed concentrated mattress dust.

Twenty-five children showed positive reactions to tobacco. Twenty-three of these gave reactions to dust within the range of plus-minus to 3 plus. The remaining 2 children (8 per cent) had completely negative reactions.

One hundred and twenty children reacted negatively to tobacco. Of these, 100 gave reactions to dust within the range of plus-minus to 3 plus. The remaining 20 (16 per cent) had completely negative reactions.

In summary it may be seen that the incidence of reactions to dust (ranging from plus-minus to 3 plus) in the children with positive and in those with negative reactions to tobacco was 92 and 84 per cent, respectively. This clearly indicates that there is no correlation between the cutaneous reaction to dust and the reaction to tobacco antigen.

THE ALLERGIC CHILD

This group consisted of 164 allergic children: 72 with asthma without pollen allergy; 6 with urticaria, migraine and vasomotor rhinitis, and 86 with pollen allergy (pollen asthma with or without hay fever, perennial asthma with pollen allergy or seasonal hay fever).

A. Cutaneous Reactions to Tobacco.—The number and incidence of intradermal reactions to Burley, Maryland, Virginia and Xanthis tobaccos in the allergic children comprising this series is shown in table 3.

It is obvious from table 3 that Virginia tobacco is less potent than the other tobaccos employed. In view of the relatively large number

of positive reactions obtained with tobaccos in this group of children, the lower potency of the Virginia variety is more strikingly evident than with the nonallergic control group.

B. Age and Sex Incidence.—Figure 2 shows the incidence of positive reactions to tobacco and pollen in the 164 allergic children (104 boys and 60 girls) with relation to age and sex. From this chart it is evident that the incidence of positive reactions to tobacco in boys and girls was 68 and 72 per cent, while the corresponding incidence of positive reactions to pollen was 67 and 73 per cent, respectively, the figures indicating that no difference existed between the sexes, which is in agreement with the observations on the group of children used as a control. There were so few subjects between the ages of 2 and 5 years that the curves recording these patients should be discarded as not representative.

TABLE 3.—*Incidence of Intracutaneous Reactions to Burley, Maryland, Virginia and Xanthis Tobaccos in 164 Allergic Children*

	Number of Reactions				Percentage of Reactions			
Cutaneous Reactions	Burley	Maryland	Virginia	Xanthis	Burley	Maryland	Virginia	Xanthis
1 plus	43	52	54	52	26.2	31.7	32.9	31.7
2 plus	19	14	10	17	11.6	8.5	6.1	10.3
3 plus	20	18	7	13	12.2	11.0	4.2	8.0
1-3 plus	82	84	71	82	50.0	51.2	43.2	50.0
Plus-minus	28	26	30	24	17.1	15.9	18.4	14.6
Total positive	110	110	101	106	67.1	67.1	61.6	64.6
Negative	54	54	63	58	32.9	32.9	38.4	35.4
Total	164	164	164	164	100.0	100.0	100.0	100.0

With reference to age, it appears that in the group of children between 6 and 9 years of age the incidence of positive reactions to tobacco and the corresponding incidence of positive reactions to pollen ranged from 50 to 60 per cent. In the age period between 10 and 15 years the incidence of positive reactions to tobacco and pollen rose to as high as 80 per cent, except for a drop in the pollen reactions to 62 per cent in the age period ranging from 12 to 13 years.

The distribution of cutaneous reactions to tobacco and pollen in relation to the allergic conditions which occurred in these children is of interest. In the group of children with pollen allergy the incidence of positive reactions to tobacco in boys and girls was 89 and 84 per cent, respectively, and the corresponding incidence of positive reactions to pollen was 94 and 100 per cent, respectively.

In the group of children without pollen allergy, the incidence of positive reactions to tobacco in boys and girls was 46 and 55 per cent, respectively, and the corresponding incidence of positive reactions to pollen was 77 and 75 per cent, respectively.

From the foregoing statements it can be concluded that the incidence of positive reactions to tobacco closely paralleled the number of positive reactions to pollen and that was definitely higher in the children with than in those without clinical pollen allergy. There was no difference between the sexes. One may therefore almost predict, when testing children with pollen allergy, that positive reactions to tobacco allergens will be obtained.

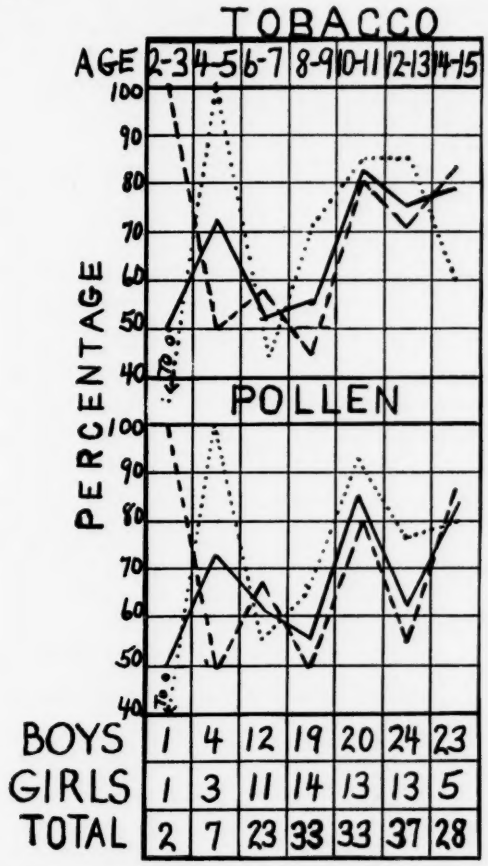

Fig. 2.—Comparative incidence of positive reactions obtained with solutions of tobacco and of pollen in 164 allergic children with relation to age and sex.

C. Relation Between Cutaneous Reactions to Pollen and Those to Tobacco.—The distribution of reactions to biologic pollen groups (ragweed or grass or both) in relation to the reactions to tobacco was as follows:

Twenty-two children allergic to pollen and 14 who were not showed positive pollen reactions to ragweed only. Twenty (91 per cent) of the

former and 11 (or 79 per cent) of the latter group showed positive reactions to tobacco. Thus, of a total of 36 allergic children with positive reactions to ragweed alone, 31 (86 per cent) showed positive reactions to tobacco.

Two children with and 4 without pollen allergy showed positive pollen reactions to grasses only. One of the 2 allergic and all of the patients nonallergic to pollen showed positive reactions to tobacco. Thus, of a total of 6 allergic children with positive pollen reactions to grasses, only 5 (83 per cent) showed positive reactions to tobacco.

Fifty-six children with and 16 without pollen allergy showed positive reactions to both ragweed and grasses. Fifty-three children (95 per cent) of the former and all (100 per cent) of the latter group showed positive reactions to tobacco. Thus, of a total of 72 allergic children with positive reactions to both ragweed and grasses, 69 (96 per cent) showed positive reactions to tobacco.

Six children with and 44 without pollen allergy showed negative reactions to pollen. Two of the former (33 per cent) and 8 (18 per cent) of the latter group showed positive reactions to tobacco. Thus, of a total of 50 allergic children with negative reactions to pollen, 10 (20 per cent) showed positive reactions to tobacco.

From the foregoing data it can be stated that of a total of 164 allergic children 114 gave positive reactions to pollens. These were grouped as follows: Eighty children were allergic to pollen and 34 were not. Seventy-four (92.5 per cent) of the former and 31 (91 per cent) of the latter group showed positive reactions to tobacco. Thus, of a total of 114 allergic children with positive reactions to pollen, 104 (92 per cent) showed positive reactions to tobacco. Of the 50 children with negative reactions to pollen, 10 (20 per cent) showed positive reactions to tobacco.

The incidence of positive reactions to tobacco in the allergic children with positive cutaneous reactions to pollen was approximately the same with either ragweed or grass pollen and was similar to the incidence recorded for the children used as controls. The impression that positive reactions to tobacco are more apt to occur with positive reactions to ragweed than with positive reactions to grass pollen is erroneous. This perhaps is due to the overwhelming preponderance of positive cutaneous reactions to ragweed as compared with those to grass (9:1) when these pollens reacted independently of each other. For this reason, in various tables in this paper in which tobacco and pollen reactions are studied comparatively no special column is set aside for either pollen.

The incidence of positive reactions to tobacco in allergic children with positive cutaneous reactions to both ragweed and grass pollen (96 per cent) was higher than in those with reactions to either ragweed

(86 per cent) or grass (83 per cent) alone. This finding suggests that in the presence of cutaneous reactions to multiple pollens the incidence of positive reactions to tobacco will invariably increase.

D. Comparative Incidence of Reactions to Tobacco and to Pollen.—Table 4 is a summary of the comparative incidence of intradermal reactions to tobacco and to pollen in allergic children.

It can be observed in table 4 that the reactions to tobacco which ranged from 1 to 3 plus comprised those of about 58 per cent of the 164 allergic children and that the corresponding positive reactions to pollen occurred in 94 per cent of this group. The plus-minus reactors to tobacco comprised 11.6 per cent, and the corresponding reactors to pollen 79 per cent, of the group. The percentage of positive reactions

TABLE 4.—*Comparative Incidence of Intracutaneous Reactions to Tobacco and to Pollen in 164 Allergic Children* *

Cutaneous Reactions	Tobacco Reactions		Pollen										
			Number of Reactions					Percentage of Reactions					
			Negative		Positive			Negative		Positive			Total Positive
	No.	%	−	±	+	++	+++	−	±	+	++	+++	
1 plus	50	30.5	1	4	18	3	24	2	8	36	6	48	90
2 plus	20	12.2	0	1	6	2	11	0	5	30	10	55	95
3 plus	25	15.2	0	0	4	4	17	0	4	16	16	68	96
1-3 plus	95	57.9	1	5	28	9	52	1	5	29	10	55	94
Plus-minus	19	11.6	3	1	4	3	8	16	5	21	16	42	79
Total positive	114	69.5	4	6	32	12	60	4	5	28	11	52	91
Negative	50	30.5	38	2	3	0	7	76	4	6	0	14	20
Total	164	100.0	42	8	35	12	67	26	5	21	7	41	69

* See footnotes to table 2.

to pollen (94 per cent) in the children who showed 1 to 3 plus reactions to tobacco was somewhat higher than in the group of children (79 per cent) with plus-minus reactions to tobacco. Nevertheless, the incidence of the positive reactions to pollen in the latter group was too high to lack significance, especially in view of the fact that it was approximately that found in the group of children used as controls.

To summarize the data just cited: The total incidence of positive reactions to tobacco in 164 allergic children was 69.5 per cent, and the corresponding incidence of positive reactions to pollen was 91 per cent, while in the 50 children with totally negative reactions to tobacco the incidence of positive reactions to pollen was 20 per cent. These figures indicate that the positive reaction to tobacco is more closely tied up with the positive reaction to pollen than the reaction to pollen with the reaction to tobacco.

E. Reactions to Tobacco in Children With and Without Pollen Allergy.—In the preceding section we analyzed in detail the comparative incidence of tobacco and of pollen reactions in allergic children, irrespective of the presence or absence of pollen allergy. We shall now analyze the incidence of tobacco reactions in 164 children with and without pollen allergy (table 5).

As seen in table 5, the incidence of the tobacco reactions which ranged from 1 to 3 plus in the children with and in those without pollen

TABLE 5.—*Comparative Incidence of Intracutaneous Reactions to Tobacco and to Pollen in 78 Asthmatic Children Without Pollen Allergy and in 86 Children with Pollen Allergy* *

Cutaneous Reactions	Tobacco† Reactions		Pollen†										
			Number of Reactions					Percentage of Reactions					
			Negative		Positive			Negative		Positive			Total Positive
	No.	%	—	±	+	++	+++	—	±	+	++	+++	
Pollen Allergy													
1 plus	29	34.0	0	2	7	1	19	0.0	6.9	24.1	3.5	65.5	93.1
2 plus	12	14.0	0	0	2	1	9	0.0	0.0	16.7	8.3	75.0	100.0
3 plus	24	28.0	0	0	4	4	16	0.0	0.0	16.7	16.7	66.6	100.0
1-3 plus	65	76.0	0	2	13	6	44	0.0	3.0	20.0	9.0	68.0	97.0
Plus-minus	10	11.0	0	0	1	2	7	0.0	0.0	10.0	20.0	70.0	100.0
Total positive	75	87.0	0	2	14	8	51	0.0	2.7	18.6	10.7	68.0	97.3
Negative	11	13.0	3	1	2	0	5	27.2	9.1	18.2	0.0	45.5	63.7
Total	86	100.0	3	3	16	8	56	3.5	3.5	18.6	9.3	65.1	93.0
Asthma Without Pollen Allergy													
1 plus	21	26.9	1	2	11	2	5	4.8	9.5	52.4	9.5	23.8	85.7
2 plus	8	10.3	0	1	4	1	2	0.0	12.5	50.0	12.5	25.0	87.5
3 plus	1	1.3	0	0	0	0	1	0.0	0.0	0.0	0.0	100.0	100.0
1-3 plus	30	38.5	1	3	15	3	8	3.3	10.0	50.0	10.0	26.7	86.7
Plus-minus	9	11.5	3	1	3	1	1	33.3	11.1	33.3	11.1	11.1	55.5
Total positive	39	50.0	4	4	18	4	9	10.3	10.3	46.1	10.3	23.0	79.4
Negative	39	50.0	35	1	1	0	2	89.7	2.6	2.6	0.0	5.1	7.7
Total	78	100.0	39	5	19	4	11	50.0	6.4	24.4	5.1	14.1	43.6

* Six children with urticaria, migraine and vasomotor rhinitis are included.
† See footnotes to table 2.

allergy was 76 and 38.5 per cent, respectively, while the corresponding incidence of positive reactions to pollen was 97 and 87 per cent, respectively.

The incidence of the plus-minus reactions to tobacco in the children with and in those without pollen allergy was 11 and 11.5 per cent, respectively, while the incidence of corresponding positive reactions to pollen was 100 and 56 per cent. This indicates that the plus-minus as well as the 1 to 3 plus reactions to tobacco more closely paralleled the positive cutaneous reactions to pollen in the children with than in those without pollen allergy.

The total incidence of positive reactions to tobacco in the children with and in those without pollen allergy was 87 and 50 per cent, respectively, while the incidence of the corresponding positive reactions to pollen was 97 and 79 per cent, respectively. Thus, the incidence of positive reactions to tobacco rose sharply in the children with active pollen sensitization as compared with the incidence in those without pollen allergy. Moreover, the relatively high incidence of positive reactions to tobacco occurring in the latter group of children obviously paralleled the corresponding positive cutaneous reactions to pollen.

The incidence of negative reactions to tobacco in the children with and in those without pollen allergy was 13 and 50 per cent, respectively, while the incidence of the corresponding positive reactions to pollen was 64 and 8 per cent, respectively. The incidence of 64 per cent of positive reactions to pollen in the children with pollen allergy probably would have been higher were it not for the fact that in this group there were 4 children with pollen allergy who were refractive to pollen by cutaneous test. In these children the reactions obtained with the ophthalmic test with dry pollen were positive.[12]

From the foregoing data it can be stated that in the children with clinical pollen allergy the cutaneous reaction to tobacco was more closely bound with the positive cutaneous reaction to pollen than vice versa. In the children without pollen allergy the positive reaction to tobacco was also closely parallel to the positive cutaneous reaction to pollen. The negative reaction to tobacco was associated, curiously, with the negative reaction to pollen. This finding was similar to that of the control series.

In reviewing the degree of cutaneous reactions (table 5) in the group with pollen allergy, one notes an appreciable number of 1 plus and a few negative cutaneous reactions to pollen. With the omission of a small number of children who were refractive to pollen by cutaneous test, the reactions were largely due to the fact that these children had been under intensive specific pollen treatment for varying periods when the tobacco tests were performed. The influence of intensive specific therapy, to the extent even of abolishing an initially positive cutaneous reaction to pollen, is well known to some workers and has been reported by one of us.[13]

The incidence of positive reactions to tobacco in a group of allergic patients varies with the number who have pollen allergy. When the patients with this allergy are in the majority, the incidence of positive reactions to tobacco will be higher than in a series in which such patients are in the minority. The incidence of positive reactions to tobacco is

12. Peshkin, M. M.: A Dry Pollen Ophthalmic Test in Pollen Asthma and Hay Fever Patients Negative to Cutaneous Tests, J. Allergy **3**:20 (Nov.) 1931.

13. Peshkin, M. M.: Critique of the Perennial Treatment of Pollen Allergy, J. Allergy **7**:477 (July) 1936.

lower in allergic patients with positive cutaneous reactions to pollen without pollen allergy than that found in an equal number of patients with active pollen allergy. In this study the number of patients with active pollen allergy was approximately the same as the number without it (table 5).

Observations were made on 12 allergic children who gave negative reactions to both tobacco and pollen. When these children were retested, eighteen months later, it was found that half of them had positive cutaneous reactions to tobacco and, curiously, positive reactions to pollen for the first time. These children did not show any symptoms of pollinosis.

A group of 14 children with pollen allergy who had positive cutaneous reactions to pollen and negative reactions to tobacco on being retested eighteen months later likewise had positive reactions to tobacco.

This suggests that a certain proportion of allergic children without pollen allergy and almost all those with the allergy who have negative reactions to tobacco may eventually acquire positive reactions. This emphasizes in a different manner the previous observations as to the close relation between the cutaneous reactions to tobacco and those to pollen.

GENERAL (CONSTITUTIONAL) REACTIONS TO INTRACUTANEOUS TESTS

It has previously been stated that the concentrated tobacco extract (0.1 mg. of nitrogen per cubic centimeter) is a relatively poor antigen, in this respect resembling extract of house dust. The occurrence of an immediate general reaction to the routine tests with tobacco has not been reported in the literature. Harkavy [14] found no general reactions to tobacco tests in 1,200 adults. No general reactions were encountered with the pollen tests, largely owing to the technic of testing, which has been described in this paper.

In this study 3 children (2 of the allergic and 1 of the normal group) experienced general reactions immediately after intradermal tests with tobacco antigen. Each of these children showed a 3 plus reaction to one or all of the tobacco extracts. All children had negative reactions to tobacco with the scratch test. The general reactions were easily controlled with epinephrine hydrochloride (1 : 1,000 solution).

S. F., a boy aged 8 years, had pollen asthma with hay fever (ragweed). Reactions to tests with Burley, Maryland, Virginia and Xanthis tobacco were negative in 1935. The scratch test gave positive reactions to ragweed and grass. When tests were repeated eighteen months later the reactions to tobacco ranged from 2 to 3 plus. The intradermal test gave a 1 plus reaction to ragweed and a 2 plus reaction to grass (0.01 mg. of nitrogen per cubic centimeter). Five minutes after the intradermal tests the child sneezed and the eyes reddened, symptoms soon followed by a spasmodic cough and an attack of asthma. On one arm the sites of the tobacco reactions became markedly inflamed and swollen, while on

14. Harkavy, J.: Personal communication to the authors.

the other arm the pollen reactions remained unchanged. Passive transfer tests were made with 2 recipients. The blood was collected shortly after the general reaction, and the results of the tests were negative.

H. S., a boy aged 14 years, had asthma with hay fever (ragweed and grass). The intradermal tests with pollens were not made. Five minutes after the tobacco tests the patient began to sneeze; the eyes reddened, and nasal blocking soon followed, with wheezing and a moderately severe attack of asthma. Passive transfer tests with all four tobaccos and with ragweed and grass pollen gave positive reactions.

H. R., a boy aged 6 years, was nonallergic and belonged to the control series. The intradermal tests to pollens (0.2 mg. of nitrogen per cubic centimeter) gave negative results. Ten minutes after the tests to tobacco the sites were markedly swollen and red; the patient began to sniffle; the eyes became red, and marked nasal blocking was followed by a short spasmodic, dry cough. The chest was free from all asthmatic rales. Passive transfer tests gave positive reactions to the tobaccos and negative reactions to ragweed and grass pollen.

It is of interest to note that these children, as well as all the allergic children in this study, at no time showed any clinical evidences of intolerance to the usual exposure to tobacco. It should be borne in mind that each child in this study was tested with four concentrated tobacco extracts at one sitting.

LOCAL PASSIVE TRANSFER

Fifty children (46 allergic and 4 nonallergic) with varying degrees of reaction to tobacco, ranging from negative to 3 plus, were selected for passive transfer.

A. Allergic Children.—In table 6 is a protocol of the reactions of 46 allergic children to tests with Burley, Maryland, Virginia and Xanthis tobaccos and to ragweed and grass pollen by the direct and the indirect method.

Table 6 shows that there were 39 patients with positive reactions to tobacco by direct test. Twenty-eight patients (72 per cent) showed positive reactions to the indirect test. All these 28 patients showed positive reactions to pollens with the direct test, and with the indirect test only 3 reacted negatively (cases 17, 19 and 22).

The remaining 11 patients (28 per cent) who had positive reactions to tobacco by direct test showed negative reactions with the indirect test. Ten of these patients showed positive reactions to pollen by direct test, and 5 of them showed positive reactions with the indirect test. The eleventh patient showed negative reactions to pollen with both methods of testing.

Seven patients showed negative reactions to tobacco with the direct and with the indirect method of testing. Five of the 7 patients showed positive reactions to pollen with the direct test, and 4 of the 5 patients showed positive reactions with the indirect test.

A review of table 6 shows that Virginia tobacco is antigenically weaker with the direct and the indirect method of testing than the

TABLE 6.—*Comparison of Intradermal Reactions with the Direct and the Indirect (Local Passive Transfer) Method of Cutaneous Testing with Tobacco and Ragweed and Grass Pollen in 46 Allergic Children*

Case No.	Age	Sex	Direct Method: Tobacco: Burley	Direct Method: Tobacco: Maryland	Direct Method: Tobacco: Virginia	Direct Method: Tobacco: Xanthi	Direct Method: Pollen: Ragweed	Direct Method: Pollen: Grass	Indirect Method: Tobacco: Burley	Indirect Method: Tobacco: Maryland	Indirect Method: Tobacco: Virginia	Indirect Method: Tobacco: Xanthi	Indirect Method: Pollen: Ragweed	Indirect Method: Pollen: Grass
Asthma Without Pollen Allergy														
1	9	M	—	—	—	—	—	—	—	—	—	—	—	—
2	11	M	—	—	—	—	—	—	—	—	—	—	—	—
3	11	M	—	—	—	—	3+	—	—	—	—	—	1+	—
4	12	F	—	—	—	—	3+	—	—	—	—	—	—	—
5	13	M	±	±	±	±	—	—	—	—	—	—	—	—
6	15	M	1+	1+	±	±	3+	3+	±	±	±	±	2+	1+
7	12	M	1+	1+	1+	1+	1+	1+	±	±	±	—	1+	—
8	7	M	1+	1+	1+	1+	3+	1+	—	—	—	—	1+	—
9	15	M	1+	±	1+	±	2+	1+	—	—	—	—	—	—
10	10	F	1+	1+	1+	1+	1+	1+	—	—	—	—	—	—
11	10	M	2+	2+	2+	2+	1+	±	—	—	—	—	—	—
12	6	F	1+	2+	1+	2+	1+	±	1+	1+	—	1+	±	—
Ragweed Pollen Asthma With or Without Hay Fever														
13	15	F	—	—	—	—	1+	1+	—	—	—	—	1+	—
14	11	F	—	—	—	—	3+	—	—	—	—	—	1+	—
15	11	F	±	±	±	±	3+	2+	±	±	±	±	1+	±
16	6	M	±	±	±	1+	3+	±	—	—	—	—	±	—
17	14	M	1+	1+	1+	1+	2+	—	—	1+	—	—	—	—
18	14	M	1+	1+	1+	1+	1+	±	1+	1+	1+	2+	±	—
19	12	F	1+	1+	±	1+	1+	1+	±	±	—	1+	—	—
20	7	F	3+	1+	1+	1+	1+	1+	1+	1+	1+	1+	1+	±
21	8	M	3+	3+	2+	2+	3+	3+	—	—	—	—	—	—
22	13	M	2+	2+	1+	2+	1+	2+	1+	1+	±	1+	—	—
23	15	M	2+	2+	2+	2+	2+	2+	±	±	±	±	±	±
24	12	F	3+	3+	1+	3+	3+	—	2+	±	—	1+	3+	—
25	14	M	3+	3+	3+	3+	1+	±	2+	1+	1+	2+	1+	—
26	10	M	3+	3+	2+	3+	3+	—	1+	1+	±	1+	±	—
27	15	M	2+	2+	1+	1+	3+	1+	—	—	—	—	3+	—
Ragweed and Grass Pollen Asthma With or Without Hay Fever														
28	11	M	±	1+	±	1+	3+	3+	±	1+	±	1+	1+	±
29	14	M	2+	1+	1+	1+	3+	3+	—	—	—	—	3+	2+
30	14	M	3+	3+	3+	3+	3+	3+	2+	1+	±	1+	1+	1+
31	9	M	3+	3+	1+	2+	3+	1+	2+	3+	1+	2+	2+	—
32	11	F	3+	3+	3+	3+	3+	3+	3+	3+	1+	3+	3+	1+
33	15	M	3+	3+	1+	2+	3+	3+	2+	1+	±	1+	1+	1+
34	10	M	2+	3+	1+	2+	3+	3+	2+	2+	2+	2+	1+	3+
35	14	M	3+	3+	3+	3+	3+	3+	1+	1+	1+	1+	2+	1+
36	14	M	2+	3+	1+	2+	3+	3+	1+	2+	1+	2+	2+	2+
37	11	M	3+	2+	1+	3+	2+	2+	2+	3+	1+	2+	1+	1+
Ragweed Hay Fever														
38	10	F	±	—	—	±	±	3+	—	—	—	—	—	2+
													—	3+
39	15	M	—	±	±	—	3+	±	—	—	—	—	3+	—
40	14	M	±	1+	1+	1+	3+	3+	1+	1+	1+	1+	3+	3+
41	14	F	1+	1+	1+	1+	3+	3+	±	—	—	—	3+	3+
42	11	M	2+	1+	2+	2+	3+	1+	1+	1+	±	±	±	—
43	13	F	3+	3+	2+	3+	3+	3+	1+	2+	1+	1+	2+	3+
Grass Hay Fever														
44	14	M	—	—	—	—	3+	3+	—	—	—	—	±	±
45	13	M	3+	3+	±	3+	1+	1+	1+	1+	1+	1+	1+	±
Ragweed and Grass Hay Fever														
46	12	M	3+	3+	1+	2+	1+	1+	1+	2+	±	1+	1+	—

other tobaccos, which are of about equal potency. This finding is of some importance if testing is done only with Virginia tobacco.

In the selection of suitable recipients for passive transfer tests, the serums of 6 adults were subjected to transfer studies. Three showed positive and 3 negative reactions to tobacco with the direct test. In all 6 persons negative reactions were obtained by passive transfer.

A summary of the reactions to ragweed and to grass pollen with the direct and the indirect method of testing (table 6) shows that the plus-minus and the negative reactions were not transferred. On the other hand, the corresponding reactions ranging from 1 to 3 plus were obtained on passive transfer with progressively increasing frequency—ragweed: 1 plus reactions, 67 per cent; 2 plus reactions, 50 per cent, and 3 plus reactions, 91 per cent; grasses: 1 plus reactions, 17 per cent; 2 plus reactions, 75 per cent and 3 plus reactions, 93 per cent. This clearly indicates that passive transfer of the 1 plus reaction with grass pollen

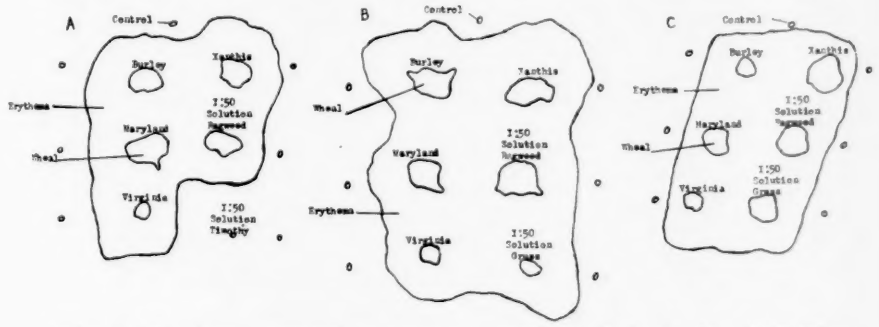

Fig. 3.—Tracings representing cutaneous reactions obtained with the indirect (local passive transfer) method of testing. Solutions of tobacco and of pollen were used. *A* indicates the results in case 31, table 6; *B*, those in case 32, and *C*, those in case 36.

is not as readily obtained as that with ragweed pollen. The total percentage of positive reactions obtained by passive transfer with ragweed was 81 per cent and that with grasses 61 per cent. Tracings representing cutaneous reactions to tobacco and pollen extracts obtained by passive transfer are shown in figure 3.

A review of table 7 shows that the total number of plus-minus reactions to tobacco obtained with the direct method in the 46 cases previously cited was 24. Of these, 42 per cent were positive with the indirect (passive transfer) method of testing. This finding is of importance and of primary significance. It is additional proof of the fact that plus-minus reactions obtained with tobacco by direct test are true positive reactions, since they can be transferred passively according to the Prausnitz-Küstner method of testing. This, however, does not imply that a negative reaction obtained with the serum by passive transfer negates

the immunologic significance of the plus-minus reaction, for it is well known that even in case of such potent allergens as pollens negative passive transfer reactions are not infrequently encountered with the serums of patients who have active pollen allergy.[15]

The total number of 1, 2 and 3 plus reactions obtained with the direct method of testing was 56, 31 and 41, respectively. Of these, 55, 71 and 95 per cent, respectively, were transferred.

Thus, of a total of 152 positive reactions obtained with all the tobaccos employed by the direct method, 102, or 67 per cent, were obtained by passive transfer.

All the negative reactions obtained with tobacco by the direct test were also negative with passive transfer.

B. Nonallergic Children.—Passive transfer studies to determine the incidence of tobacco and pollen reagins were carried out with the serums

TABLE 7.—*Summary of the Corresponding Intradermal Reactions with the Direct and the Indirect (Local Passive Transfer) Method of Testing with Burley, Maryland, Virginia and Xanthis Tobaccos in 46 Children with Allergy, Each Reaction Being Counted Separately*

	Direct Method		Indirect Method											
			Number of Reactions						Percentage of Reactions					
				Positive				Total		Positive				Total
Cutaneous Reactions	No. of Reactions	% of Reactions	Negative	±	+	++	+++	Positive	Negative	±	+	++	+++	Positive
Plus-minus.....	24	16	14	8	2	0	0	10	58	33	9	0	0	42
1 plus.....	56	36	25	11	18	2	0	31	45	20	32	3	0	55
2 plus.....	31	20	9	7	10	4	1	22	29	23	32	13	3	71
3 plus.....	41	27	2	2	21	12	4	39	5	5	51	29	10	95
Total positive...	152	100	50	28	51	18	5	102	33	18	34	12	3	67
Total negative..	32	100	32	0	0	0	0	0	100	0	0	0	0	0

from 4 children of the normal series used as controls. The receptors were other nonreacting normal children.

CASE 1.—B. B., a boy aged 7 years, showed by the direct method of testing 1 plus reactions to all the tobacco and pollen extracts employed. By passive transfer, plus-minus reactions were obtained with Burley and Maryland tobacco, 1 plus reactions with Virginia and Xanthis tobaccos and negative reactions with ragweed and grass pollens.

CASE 2.—H. R., a boy aged 6 years, had 3 plus reactions to Burley and Maryland tobaccos, 2 plus reactions to Virginia and Xanthis tobaccos and negative reactions to ragweed and grass pollens. Passive transfer produced 2 plus reactions to Burley, Maryland and Virginia tobaccos, and 1 plus reactions to Xanthis tobacco and negative reactions to ragweed and grass pollens. The concentration of reagins for Burley tobacco was sufficiently marked to enable us to obtain a positive reaction with a 1:10 dilution of serum.

15. Peshkin, M. M., and Fineman, A. H.: A Comparative Study of the Direct and Indirect (Local Passive Transfer) Methods of Skin Testing with the Scratch and Intradermal Technics, Am. J. Dis. Child. **37**:39 (Jan.) 1929.

CASE 3.—R. B., a girl aged 7 years, showed by direct test 1 plus reactions to all the tobaccos and 2 plus reactions to ragweed and grass pollens. By indirect test only Burley tobacco produced a positive plus-minus reaction. A plus-minus reaction was obtained with ragweed, while the reaction to grass pollen was not transferred.

CASE 4.—D. B., a girl aged 8 years, showed negative reactions to all the tobaccos, as well as ragweed. She gave a 3 plus reaction to grass pollen. Negative reactions, except to the grasses, resulted on passive transfer.

COMMENT

From the findings recorded in this study it is obvious that the cutaneous reactions to tobacco in allergic children with pollen sensitization run parallel with and definitely higher than those in nonallergic children. The immunologic significance of these tobacco reactions is evident from the fact that in the children who reacted to tobacco, 72 per cent of the reactions were transferred passively.

The positive transferred reactions fulfilled the criteria generally recognized as necessary for identification of the immune reactions. The clinical significance of these reactions, however, is an entirely different matter. As is well known, a reaction to any allergen, whether it is a reliably studied and potent one, such as pollen, or is less active, is not etiologically diagnostic unless it can be proved that contact with a reacting allergen will elicit, or removal of the allergen will eliminate, the patient's symptoms. Since none of our children presented any clinical symptoms, this method of identification could not be applied. Nevertheless, the immunologic features of tobacco, which were clearly demonstrated in our investigation, demand some explanation. Is inhalation alone sufficient to produce cutaneous reactions in allergic children, who, according to current beliefs, have in large measure the inherent capacity to become sensitized and give reactions as a result of contact? This concept is negated by our finding that allergic children not clinically sensitive to pollen had a decidedly lower percentage of positive cutaneous reactions to tobacco than those who were sensitive to pollen. It follows, therefore, that factors other than exposure must be involved.

The close parallelism between the positive cutaneous reactions to pollen and those to tobacco may possibly serve as a clue to the interpretation of the tobacco reactions which we obtained. On the one hand, the question of a common chemical radical in the pollen and the tobacco antigen cannot be overlooked, and, on the other hand, the possibility of a common factor in the passive transfer antibody which reacts with both ragweed and grass pollens as well as with tobacco must be entertained. Some light as to the latter may be derived from the work of Romanoff,[16]

16. Romanoff, A. J.: Studies in Antigen Relationship of Ragweed, Tobacco and Pyrethrum, to be published.

who found that ragweed pollen might exhaust the tobacco reagin whereas the tobacco allergen did not exhaust the ragweed reagin in the cases which he reported. Here too, however, there is danger in drawing any definite conclusions, because it is possible that the concentration of the ragweed reagin in the particular patients studied by Romanoff may have been higher than that of the tobacco reagin. Further elucidation of this problem must await additional investigation.

From our studies, however, we have definitely established that the tobacco reactions cannot be regarded as chance irritations and of nonspecific character, as was postulated by Chobot.[6] It is impossible to draw conclusions from his few unsuccessful attempts at passive transfer with serums obtained from 4 selected subjects, especially since he used Virginia tobacco, which we have shown to be the weakest of the tobacco antigens. Nor is it logically possible to ascribe a histamine-like effect to tobacco: Chobot himself clearly stated that experimental study on guinea pigs failed to elicit reactions characteristic of histamine.

Since our present investigation deals primarily with cutaneous reactions to tobacco in children, our observations in no way conflict with the findings of Harkavy and Sulzberger and their co-workers in their studies on tobacco hypersensitiveness in smokers with vascular disease. Credit should be given these workers for calling attention to the fact that the specificity of tobacco is dependent on the protein moiety rather than on any of the toxic substances.

SUMMARY

Two hundred nonallergic and 164 allergic children (86 with and 78 without pollen allergy), ranging in age from 2 to 15 years, and 67 adults with no personal history of allergy were tested with Burley, Maryland, Virginia and Xanthis tobaccos and with ragweed and grass pollen. Dry powdered extracts were employed as a routine in the scratch test for the allergic children. Fluid (Coca) extracts of tobacco and pollen were applied in intradermal tests when the reaction to the scratch test was negative. It was found that tobacco is a weak antigen and must be employed with the intradermal test. Fifty children were selected for local passive transfer tests (Prausnitz-Küstner method).

Intradermal reactions to tobacco ranging from plus-minus to 3 plus were found to be specific. This finding was based on the ability to transfer both the plus-minus and the plus reaction according to the classic Prausnitz-Küstner technic.

Of the four tobaccos used in our studies, Virginia tobacco proved to be relatively less active than the others.

Sex played no role in the incidence of the reactions to tobacco in the various groups tested.

The incidence of cutaneous reactions to tobacco was distributed equally between children who reacted positively to ragweed or grasses in both the allergic and the nonallergic group. Among children who reacted to both ragweed and grasses the incidence of positive reactions to tobacco was slightly raised.

Of the 200 nonallergic children used as controls, 35, or 17.5 per cent, reacted to tobacco. In the latter group 83 per cent reacted to pollen. Among the remaining 165 children, who had completely negative reactions to tobacco, the incidence of positive reactions to pollen was 5.5 per cent.

Of the 164 allergic children, 114, or 69.5 per cent, reacted to tobacco. Of the latter group 91 per cent reacted to pollen. For the remaining 50 children, who had totally negative reactions to tobacco, the incidence of positive reactions to pollen was 20 per cent. The incidence of tobacco reactions for the 86 allergic children with clinical sensitiveness to pollen was distinctly higher (87 per cent) than the incidence for 78 children who reacted to the cutaneous test for pollen but who showed no clinical evidence of pollen hypersensitiveness. Only 50 per cent of the latter reacted to tobacco. The incidence of pollen reactions for the group clinically sensitive to pollen was 97 per cent, as compared with 79 per cent for the clinically nonsensitive group. These figures indicate a striking parallelism between cutaneous reactions to tobacco and those to pollen. The positive reaction to tobacco is more closely bound up with the positive reaction to pollen than vice versa.

General (constitutional) reactions following intradermal tests with tobacco occurred in 3 children.

Seventy-two per cent of the allergic patients with positive reactions to tobacco given by direct test had positive reactions to the passive transfer test. Patients selected for the passive transfer test showed reactions to tobacco ranging from negative to 3 plus. Patients with negative reactions to the direct test did not react to the transfer test. Of the patients who showed reagins (antibodies) for tobacco, 42 per cent of those who had plus-minus reactions by direct test, 55 per cent of those giving 1 plus reactions, 71 per cent of those giving 2 plus reactions and 95 per cent of those with 3 plus reactions had positive reactions to the passive transfer test.

Of 150 nonallergic control children tested with dust and tobacco, 25 (17 per cent) reacted to tobacco, and of these 23 (92 per cent) gave from plus-minus to 3 plus reactions to dust. The remaining 125 children (83 per cent) did not react to tobacco, and of these 105 (84 per cent) showed reactions to dust. No correlation exists between tobacco antigen and dust antigen.

In the light of this study it is obvious that the tobacco reaction is specific and transferable passively and that it closely parallels the cutaneous reaction to pollen.

ACUTE EMPYEMA OF THE CHEST IN CHILDREN

A REVIEW OF THREE HUNDRED CASES

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There is reason to believe that empyema of the chest was recognized by the ancients and that the Egyptians and Chinese suggested surgical drainage after empyema necessitatis had developed. The results of treatment of empyema must have been poor even as late as 1835, when Dupuytren, the most eminent French surgeon of his day, refused operation on himself for empyema, saying that he would "rather die by the hand of God than with the aid of a physician." Until the early part of the nineteenth century it appears that treatment was directed toward drainage in the chronic stage rather than in the acute. Sporadically a method was suggested which tended to attack the disease in its acute stage, but because of the appalling mortality, the relatively poor results and the apparent magnitude of the surgical procedure, the method found few who would try it and even fewer who would advocate it. It was not until 1844 that a deliberate attempt was made to treat acute empyema. Roe,[1] in a paper delivered before the Royal Medical and Chirurgical Society of London, advocated aspiration as a therapeutic measure in the treatment of acute empyema. He reported 9 such cases, with 8 recoveries and 1 fatality. Enthusiasm for this method is evidenced in the many cases reported in the literature soon thereafter. At a later date, however, a number of cases were reported in which this method failed. As a result, other methods were sought which would yield an early and a more satisfactory evacuation of the pus. In 1859 Goodfellow and De Morgan [2] suggested intercostal drainage, and in the following year rib resection drainage was introduced.[3] It was not long

From the Departments of Surgery and Pediatrics, the Jewish Hospital.

1. Roe, H.: On Paracentesis Thoracis as a Curative Method in Empyema and Inflammatory Hydrothorax, Lancet **1**:197, 1844.

2. Goodfellow, S. J., and De Morgan, C.: On the Treatment of Empyema by "Drainage," M. Times & Gaz. **1**:659, 1859.

3. Sellor, T. H.: Surgery of the Thorax, London, Constable & Co., Ltd., 1933.

before some of the shortcomings of these methods were discovered, for soon thereafter a host of modifications were suggested. The indiscriminate use of these methods without regard for the underlying cause of the empyema or the character of the pus failed to reduce the morbidity or the mortality. Until the early part of the twentieth century rib resection drainage for the treatment of empyema was the common practice.

The influenza (Streptococcus haemolyticus) pandemic of 1918 brought up a new problem in the management of empyema. In civil practice most of the cases of empyema had been postpneumonic, and the pneumococcus was the most common offender. Empyema in these cases developed and was therefore treated after the acute pneumonic process had subsided. In the influenza pandemic the empyema developed during the pneumonia, and in many instances surgical intervention was instituted during the acute phase of the pneumonia. Modern warfare and the pandemic produced a situation which had no counterpart in past experience. During the Great War, in many military camps in the United States drainage was instituted in accordance with the experiences gained in civil practice. The unusually high mortality which followed in the wake of this procedure led to the appointment of an Empyema Commission whose responsibility it was to investigate the causes of death in influenzal empyema. The commission [4] noted that the mortality was highest in those cases in which early and open drainage was instituted and that most of the deaths were apparently due to asphyxia. Graham [5] and his co-worker Bell [6] were able to show experimentally that neither the lung nor the mediastinum was stabilized during the developmental stages of a streptococcic empyema and that an open pneumothorax at this time caused a displacement of the mediastinum into the contralateral hemithorax. As a result there was functional embarrassment of the opposite lung. They were then able to explain the patient's asphyxial death on the basis of the increased anoxemia which followed an open pneumothorax, before the mediastinum was stabilized. As further proof of this point, it was demonstrated that the mortality rate was considerably lower in those instances in which the pus was not drained by the open method until the formative stage of the pneumonia had subsided.

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4. Cases of Empyema at Camp Lee, Va.: Preliminary Report by the Empyema Commission, J. A. M. A. **71**:366 (Aug. 3); 443 (Aug. 10) 1918.

5. Graham, E. A.: Some Fundamental Considerations in the Treatment of Empyema Thoracis, St. Louis, C. V. Mosby Company, 1925.

6. Graham, E. A., and Bell, R. D.: Open Pneumothorax: Its Relation to the Treatment of Acute Empyema, Am. J. M. Sc. **156**:839, 1918.

The adherence to these principles is responsible for the decrease in mortality in empyema. The morbidity, however, still remains high. In recent years literally hundreds of methods have been devised in an attempt to decrease this morbidity. Their very number attests to the fact that no one procedure can be relied on in the management of all forms of empyema.

It is a common and mistaken belief that empyema per se in children under 2 years of age carries with it a high mortality. The oft quoted statistics of Brown,[7] Paschlau and Lehmann,[8] Steinke,[9] Wilensky[10] and many others seem to corroborate this view:

	Mortality in the First Year of Life, %	Mortality in the Second Year of Life, %
Brown	40.5	43
Paschlau and Lehmann	56 to 74	24 to 59
Steinke	71	45
Wilensky	48	31

In our own cases the total mortality in the first six months of life was 58 per cent,[11] in the second six months 50 per cent and in the second year 26 per cent (table 1). Such statistics imply a high mortality in children under 2 years of age. It is of interest to note that these rates are gross and do not take into consideration the etiologic process or organism or the complications present at the time of the institution of treatment or at the time of the patient's death. It is the purpose of this communication to show, first, that with uncomplicated empyema the mortality in children is not high; second, that the mortality varies with the severity of the complications and with the virulence of the etiologic organism, and, finally, that with uncomplicated empyema the results of surgical drainage vary with the method, the etiologic organism and the duration of the disease. To this end, we have reviewed 300 cases of empyema from the following points of view:

1. The age of the patient.

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7. Brown, J. P.: Analysis of Two Hundred and Fifty Cases of Empyema Treated at Children's Hospital in Philadelphia, Ann. Surg. **77**:401, 1923.

8. Paschlau and Lehmann, cited by Klages, F.: Ergebnisse der Behandlung des kindlichen Pleuraempyems mittels Rippenresektion und geschlossener Drainage, Zentralbl. f. Chir. **60**:627, 1933.

9. Steinke, C. R.: Acute Empyema in Children, Ann. Surg. **101**:617, 1935.

10. Wilensky, A. O.: Empyema of the Thorax, Surg., Gynec. & Obst. **20**:501, 1915.

11. Throughout this paper we have eliminated the use of the fractional percentages in our statistics and have used the whole number closest to the true figure.

2. The duration of any preceding disease and of the empyema before the diagnosis of the latter was made or before surgical treatment was instituted.

3. The method of treatment.

4. The bacterial origin of the empyema.

5. The complications present at the time of the institution of therapy.

6. Other preoperative complications which might influence the outcome in the case.

The cases for the present study were taken from the records of the Jewish Hospital of Brooklyn for patients admitted between the early part of 1929 and the latter part of 1936. In 122 of these cases the

TABLE 1.—*Mortality in Relation to the Age of the Patient and to the Etiologic Organism in 255* Cases of Empyema of the Chest in Children*

			Etiologic Organism							
			Pneumococcus		Streptococcus		Staphylococcus		Mixed Organisms	
Age, Years	No. of Cases	Total Mortality	No. of Cases	Mortality	No. of Cases	Mortality	No. of Cases	Mortality	No. of Cases	Mortality
0 -½	19	11 (58%)	5	2	3	3	11	6	..	..
½ - 1	16	8 (50%)	5	0	6	5	3	1	2	2
1 - 2	35	9 (26%)	19	7	13	2	2	0	1	0
2 - 3	42	5 (12%)	18	0	20	4	3	1	1	0
3 - 5	35	1 (3%)	18	0	7	0	4	1	6	0
5 - 7	46	9 (19%)	29	3	11	4	2	1	4	1
7 - 9	22	4 (18%)	7	0	7	2	3	1	5	1
9 -12	19	2 (11%)	8	1	6	0	3	1	2	0
12 -15	21	8 (38%)	9	4	5	2	2	1	5	1
Total	255*	57 (22%)	118	17 (15%)	78	22 (28%)	33	13 (40%)	26	5 (19%)

* In this series there were an additional 33 cases in which the etiologic organism was not determined and 12 in which surgical therapy was unsuccessful.

empyema was due to the pneumococcus, in 82 to the streptococcus, in 35 to the staphylococcus and in 28 to mixed organisms. In addition, there were 33 cases in which the etiologic organism was not determined. The last group of cases is omitted from further consideration. It is noteworthy to point out that there was but 1 death in these 33 cases and that in all treatment was by rib resection drainage. Of the 267 cases under consideration there were 12 in which surgical treatment was ultimately considered to have failed. In 4 of these the empyema was due to a pneumococcus, in 4 to a streptococcus, in 2 to a staphylococcus and in 2 to multiple organisms. These 12 cases will be discussed in more detail under their respective subheadings.

In table 1 we have tabulated the mortality with respect to the etiologic organism and the age of the patient. It will be noted that during the first year of life the gross mortality was 20 per cent for pneumococcic

empyema, 50 per cent for the staphylococcic, 89 per cent for the streptococcic and 100 per cent for empyema due to mixed infection. In the second year of life the mortality was 37 per cent for pneumococcic empyema and 15 per cent for streptococcic. There were no fatalities from staphylococcic empyema or from that due to multiple organisms. The gross mortality, therefore, in the first two years of life was 28 in 70 cases, or 40 per cent. Thus a reexamination of table 1 fails to reveal any information not previously brought out by other writers. An analysis of each group of cases, however, yields considerable additional information.

All patients in the cases included in this series had preoperative diagnostic thoracentesis with bacteriologic and cytologic studies of the fluid thus obtained. The mere presence of bacteria in a serous, serofibrinous or serohemorrhagic fluid did not constitute sufficient evidence to warrant the diagnosis of empyema. It has been repeatedly pointed out that bacteria may be present in the pleural effusion which accompanies pneumonia without the subsequent development of empyema. Our criteria for the diagnosis of empyema was the presence of a collection of frank pus in the pleural cavity. Our criteria for cure of empyema was (1) an afebrile state, (2) minimal drainage, (3) complete expansion of the lung and (4) roentgenographic evidence of complete expansion of the lung without retention of pleural fluid. Conversely, treatment was considered to have failed in those cases in which (1) the patient continued to have a febrile course, (2) drainage persisted, (3) the lung was incompletely expanded, (4) the roentgenograms showed retained fluid and (5) the patient required over ninety days of postoperative hospitalization without conforming to the aforementioned criteria for cure.

PNEUMOCOCCIC EMPYEMA

An examination of the first three charts shows that pneumococcic empyema usually occurs after the acute pneumonic process has subsided. Such empyema is said to be postpneumonic. In 31 of the 118 cases of pneumococcic empyema the diagnosis of this complication was made before the tenth day of illness, and in 38 cases it was made between the eleventh and the fourteenth day of illness. In the remaining 49 cases the diagnosis was made after the fourteenth day. (Regarding the last group of cases it must be pointed out that many of the patients were admitted to the hospital with a history suggestive of the presence of empyema following pneumonia.) In other words, in 38 of 69 known cases empyema developed after the tenth day of the primary pneumococcic pneumonia.

In the first chart we have recorded the cases in which pneumococcic empyema was treated by aspiration. It will be noted that in the cases

of uncomplicated empyema there was but 1 fatality, a mortality of 20 per cent, whereas in the 12 cases in which complications were present at the time the empyema was diagnosed there were 11 deaths, a mortality of 92 per cent. In addition, 14 patients with uncomplicated empyema treated by repeated aspiration were later subjected to rib resection drainage. On the basis of the total number of patients with uncomplicated empyema treated by aspiration the mortality was 6 per cent and the number of failures 14 (74 per cent). Of the 4 patients treated successfully, 1 was discharged on the eleventh day after the aspiration and another on the thirty-eighth day. The latter patient required six aspirations. The average length of hospitalization in the

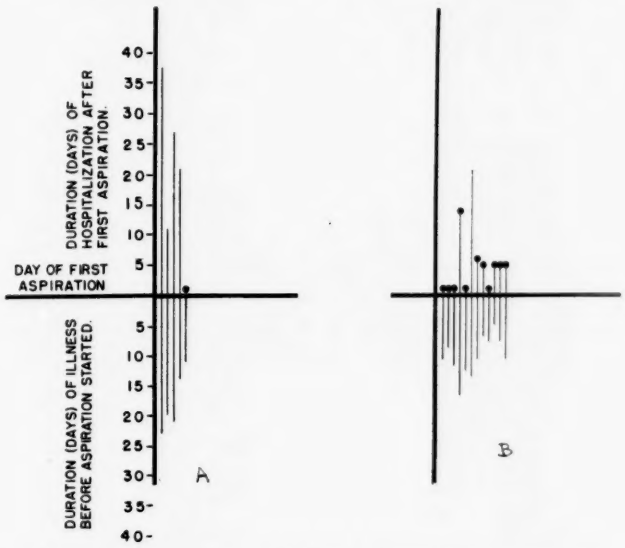

Chart 1.—Seventeen cases in which pneumococcic empyema was treated by aspiration. *A*, 5 cases of uncomplicated empyema, with 1 fatality; *B*, 12 cases of complicated empyema, with 11 fatalities. The solid dot indicates the day of death.

4 cases was twenty-four days. In the 11 cases of complicated empyema in which the patient succumbed, the complications were as follows:

Bilateral bronchopneumonia	6
Contralateral bronchopneumonia	3
Lung abscess	1
Pericarditis	1

The 1 patient who survived had a pleurobronchial fistula.

The second chart represents the relation of age to mortality and to duration of hospitalization in the cases of pneumococcic empyema treated by intercostal drainage. In this series there were 21 cases of

uncomplicated empyema with no fatality and 2 cases of complicated empyema with 1 fatality (50 per cent mortality). In addition, there were 13 cases in which the patient was treated by intercostal drainage and later required rib resection drainage. The incidence of failures with intercostal drainage was 13 in 36 cases, or 39 per cent. In 12 of these cases the condition was uncomplicated, and in 1 it was complicated by a ruptured peripheral lung abscess and a pleurobronchial fistula. Among the patients with uncomplicated empyema there were 2

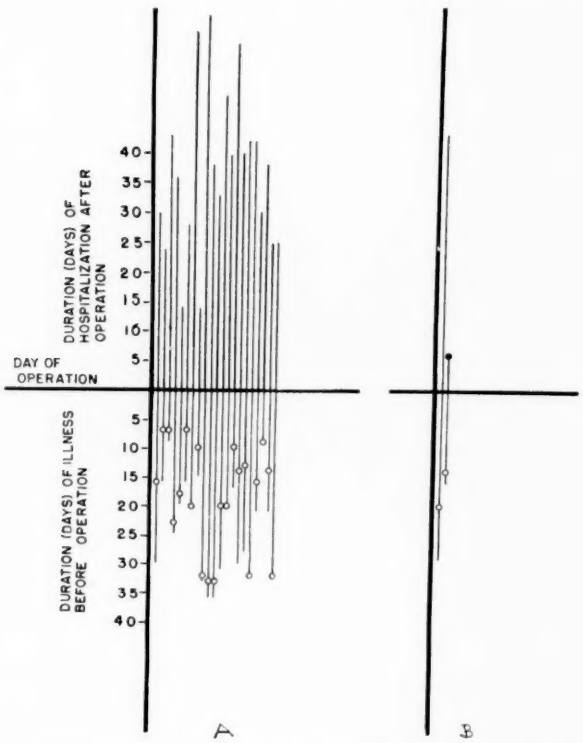

Chart 2.—Twenty-three cases in which pneumococcic empyema was treated by intercostal drainage.

In charts 2 to 9, inclusive, the small circle indicates the day empyema was diagnosed. The solid dot denotes the day of the patient's death. Each vertical line represents the course of 1 patient's illness. Each series is arranged according to age, the youngest subject being first and the oldest last. *A* represents cases of uncomplicated empyema, and *B* represents cases of complicated empyema.

who required less than two weeks of hospitalization and 7 who required over six weeks for drainage and hospitalization. The average duration of hospitalization after intercostal drainage was instituted for uncomplicated empyema was thirty-seven days. On the average, drainage was instituted on the twenty-fifth day of the patient's illness (including the

duration of illness attributed to the pneumonia). One of the 2 patients with complicated empyema had a pleurobronchial fistula; this patient survived and was discharged on the forty-third postoperative day. The other patient had a lung abscess and pneumonia on the same side as the empyema; he succumbed on the sixth postoperative day.

The third chart represents a series of 78 patients with pneumococcic empyema treated by rib resection drainage, in 67 of whom the condition was uncomplicated and in 11 complicated. There were no fatalities from the uncomplicated disease. From complicated empyema there were 4 deaths, a 36 per cent mortality. In addition to the aforemen-

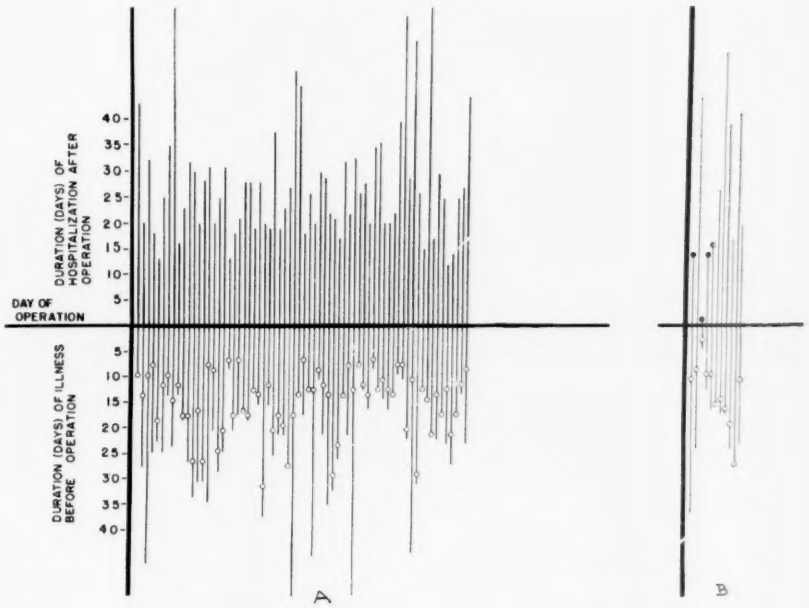

Chart 3.—Seventy-eight cases in which pneumococcic empyema was treated by rib resection drainage. See legend to chart 2.

tioned 78 patients, there were 4 (5 per cent) who failed to respond to this method of drainage. Two of these had uncomplicated empyema and had been previously treated by intercostal drainage. The other 2 patients who failed to respond to rib resection drainage had been previously treated by aspiration. One of these 2 patients had uncomplicated empyema in which the lung failed to expand, and the other had complicated empyema with a large pleurobronchial fistula.

Among the patients with uncomplicated empyema there were 4 who required less than two weeks of hospitalization and 7 who required more than six weeks of hospitalization after rib resection drainage was instituted. It is of interest to point out that 2 of these had had previous

intercostal drainage and another had had several aspirations over a period of four weeks. For 1 of the patients who was previously subjected to intercostal drainage, the duration of hospital stay after the institution of rib resection drainage was sixty-one days. This patient also required two thoracotomies. The average postoperative period of hospital care for the 67 patients with uncomplicated empyema was twenty-eight days. For the 7 surviving patients with complicated empyema the average period of hospital stay was thirty-four days. The complications in the 11 cases were as follows:

Complication	No.	Mortality
Bilateral bronchopneumonia	2	2
Lung abscess	2	..
Pleurobronchial fistula	2	..
Lung abscess and contralateral pneumonia	1	1
Pericarditis	1	1
Contralateral bronchopneumonia	1	..
Bilateral empyema	1	..
Empyema necessitatis	1	..

The patient with bilateral empyema was treated first by aspiration, then by rib resection on one side and twelve days later by rib resection drainage of the other side. The patient had an uneventful convalescence and was discharged on the forty-second day after the first rib resection.

Comment.—In the foregoing section we have reviewed 122 cases of pneumococcic empyema, in 17 of which treatment was by aspiration, in 23 by intercostal drainage and in 78 by rib resection drainage. This series also includes 4 cases in which the patient failed to respond to rib resection drainage. It was noted that of the patients treated by aspiration alone, 74 per cent failed to respond satisfactorily; of those treated by intercostal drainage 39 per cent failed to do so and of those treated by rib resection drainage in only 5 per cent was the procedure unsuccessful. Conversely, the percentage of good results was highest in the patients subjected to rib resection drainage and lowest in those treated entirely by aspiration. Furthermore, it was noted, as shown in the accompanying tabulation, that the mortality in each group, regardless of the method of treatment, was dependent on the complications present at the time treatment was instituted and not on the method of treatment or on the age of the patient.

	Percentage
All complications	22
Total mortality	14
Mortality in cases of complicated empyema	57
Mortality in cases of uncomplicated empyema	(Less than 1)

Thus, the mortality in cases of pneumococcic empyema is proportional to the incidence of complications and not to the incidence of empyema per se.

The average duration of hospital stay was greatest (thirty-seven days) for those patients who were treated by intercostal drainage, whereas for those treated by rib resection drainage it was twenty-eight days and for those treated by repeated aspiration it was twenty-four days. In considering the pros and cons of each of these methods, we note that the best way to treat uncomplicated pneumococcic empyema is by rib resection drainage. Graham and Bell [6] have shown that an opening into the pleural cavity before the mediastinum is stabilized or during the formative stage of the pneumonia is apt to prove disastrous. If need be, repeated aspirations may be performed until the pneumonia has subsided. This procedure should not be continued after the pus becomes thick. At this stage it is advisable to institute rib resection drainage. It does not seem to be in conformity with the principles of adequate drainage to expect thick, fibrinous, semiorganized coagulum to pass through an aspirating needle or even through the average intercostal tube. In fact, in several of our cases in which intercostal drainage was established the greatest difficulty encountered in management was the obstruction of the tube by the coagulum.

Our experience with irrigation of the pleural cavity as an adjuvant in the treatment of pneumococcic empyema has led us to believe that no one solution appears to possess special merits for this purpose not possessed by the others. It appears that the liquid introduced into the pleural cavity helps dislodge the adherent fibrinous masses and therefore acts mechanically rather than specifically.

With complicated empyema the problem of the treatment of the complication assumes greater importance than does the management of the empyema itself.

STREPTOCOCCIC EMPYEMA

Charts 4, 5 and 6 represent the results of various methods employed in the management of streptococcic empyema. As has been repeatedly pointed out, such empyema occurs during the acute pneumonic process and is therefore said to be synpneumonic. In 29 of the 78 cases of streptococcic empyema recorded on our charts the diagnosis was made before the tenth day of illness, in 12 between the eleventh and the fourteenth day and in the remaining 37 after the fourteenth day. As with pneumococcic empyema, many patients in the last group of cases were admitted with empyema and after the fourteenth day of illness Thus, in 29 of 41 known cases empyema developed before the tenth day of illness.

Chart 4 represents 17 cases in which streptococcic empyema was treated by aspiration. It will be noted that in the 5 cases of uncom-

plicated empyema there were 2 fatalities (40 per cent mortality), whereas in the 12 cases of complicated empyema there were 11 fatalities (92 per cent mortality). In addition, in 9 cases the patient was treated by aspiration and later subjected to another surgical procedure. Four of the cases were of uncomplicated and 5 of complicated empyema. There were failures therefore in 9 (35 per cent) of the 26 cases of streptococcic empyema in which this method was employed. Four (57 per cent of these) were among the 7 patients who survived uncomplicated empyema, and 5 (83 per cent) were among the 6 patients who

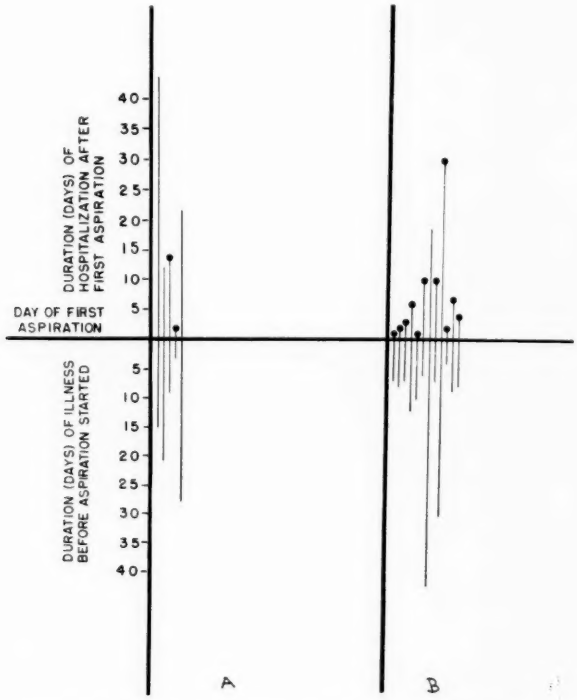

Chart 4.—Seventeen cases in which streptococcic empyema was treated by aspiration. See legend to chart 2.

survived complicated empyema. A corrected mortality on the basis of the total number of patients treated by aspiration is therefore 22 per cent for uncomplicated empyema and 65 per cent for the complicated disease.

For the 3 patients surviving uncomplicated streptococcic empyema who responded to aspiration the average period of hospitalization after treatment was begun was twenty-six days. The 1 patient surviving complicated empyema required nineteen days of hospitalization after aspiration was begun. This patient had localized empyema and empyema

necessitatis. The complications in the 12 patients treated by aspiration were as follows:

Complication	No.	Mortality
Bilateral bronchopneumonia	4	4
Bilateral bronchopneumonia and peritonitis	1	1
Bilateral pneumonia and empyema	1	1
Pericarditis and pneumonia	1	1
Pericarditis and lung abscess	1	1
Pericarditis and gangrenous bronchitis	1	1
Multiple lung abscesses	1	1
Erysipelas	1	1
Empyema necessitatis	1	..

Chart 5 correlates the incidence of fatalities with the patient's age and with the duration of hospitalization in cases in which streptococcic empyema was treated by closed intercostal drainage. In this group of 27 cases there were 5 of complicated empyema and 22 of uncomplicated empyema. Two of the latter were considered cases in which the aspiration method failed. While all the patients treated by intercostal drainage had been subjected to previous thoracenteses, only these 2 were so treated after the pus became thick. These patients had repeated aspirations over a period of thirteen and twenty-one days, respectively. The mortality for the 27 cases was 6, or 22 per cent. The mortality from uncomplicated empyema was 2 (9 per cent), whereas from complicated empyema it was 4 (80 per cent). If, in addition, we consider the 2 cases in which intercostal drainage was unsuccessful (both of which were instances of complicated empyema) the gross mortality is 20 per cent; the mortality from uncomplicated empyema remains 9 per cent, and that from the complicated disease becomes 57 per cent. The 2 patients who failed to respond to this method of drainage were (1) a patient with a pleurobronchial fistula and (2) a patient with a ruptured lung abscess and a pleurobronchial fistula. There were 2 patients with uncomplicated empyema who required less than two weeks of postoperative hospitalization and another 2 patients who required more than six weeks. The average period of hospitalization for the 20 surviving patients was twenty-eight days. One patient in this group began to have leakage about the tube on the third postoperative day and later had three communicating empyema pockets. He required sixty-nine days of hospitalization after drainage was instituted. The 1 patient surviving complicated empyema who responded to intercostal drainage required sixty days of postoperative hospitalization. On the average, drainage was instituted for the uncomplicated disease on the twenty-first day of illness, whereas for the complicated disease it was instituted on the fourteenth day. The 2 patients with uncomplicated empyema previously treated by aspiration and later subjected to intercostal drainage

required eighteen and forty-five days, respectively, of postoperative hospitalization.

The complications in the 5 cases were as follows:

Complication	No.	Mortality
Ruptured lung abscess and pleurobronchial fistula...	2	1
Pleurobronchial fistula	1	1
Bilateral empyema and pneumonia.....	1	1
Pericarditis and pneumonia.....	1	1

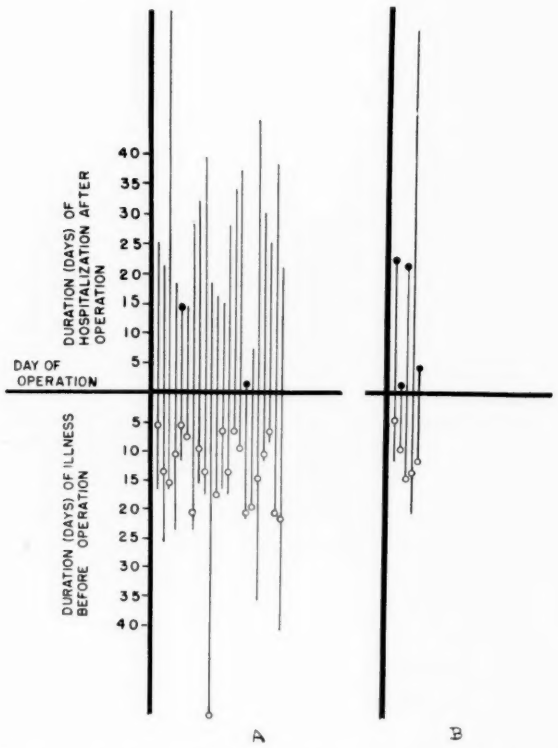

Chart 5.—Twenty-seven cases in which streptococcic empyema was treated by intercostal drainage. See legend to chart 2.

Chart 6 represents 34 cases in which the patient was treated by rib resection drainage, 28 of which were cases of uncomplicated and 6 of complicated empyema. In the former group there was 1 (4 per cent) fatality; in the latter there were 2 (33 per cent) fatalities. The mortality in the 34 cases was 9 per cent. In addition, there were 4 cases (11 per cent) in which the patient failed to respond to rib resection drainage. Three of these were cases of complicated, and 1 of uncompli-

cated, empyema. The gross mortality, therefore, on the basis of the 38 cases was 8 per cent. Calculated on the basis of the 38 cases, the mortality for uncomplicated empyema becomes 3 per cent and for complicated empyema 23 per cent. The incidence of failures for this method in cases of uncomplicated empyema therefore is 3 per cent, as compared with 33 per cent of cases of complicated empyema. It is of interest to point out that the only instance of failure of this method in the cases of uncomplicated empyema was that in a case in which the surgical

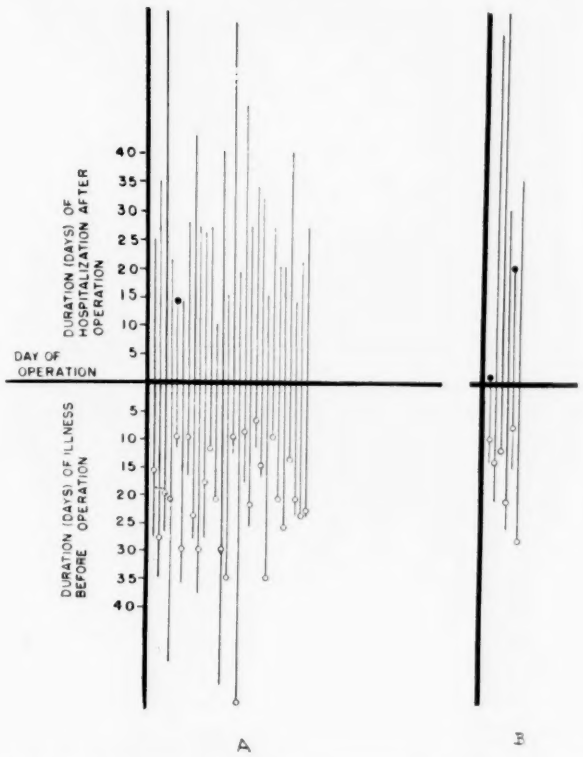

Chart 6.—Thirty-four cases in which streptococcic empyema was treated by rib resection drainage. See legend to chart 2.

wound broke down as a result of an abscess of the chest wall. The infection began at the site of an aspiration puncture and spread to the surgical wound. The 3 cases in which there were complications were (1) a case of empyema with pericarditis, (2) a case of bilateral empyema which was treated by aspiration on one side (with excellent recovery) and by rib resection drainage on the other and (3) a case of empyema with a pleurobronchial fistula.

Three of the patients with uncomplicated empyema required less than two weeks of postoperative hospitalization, and 4 required over six weeks. There were 2 who required two thoracotomies because of uneven expansion of the lung and resulting encapsulation. The average postoperative hospital stay for the 27 patients surviving uncomplicated empyema was twenty-nine days, and that for the 4 surviving complicated empyema was fifty-one days. The complications in the 6 cases were as follows:

Complication	No.	Mortality
Underlying pneumonia	1	1
Lung abscess	2	1
Spontaneous pneumothorax	1	..
Pericarditis	1	..
Ruptured peripheral lung abscess	1	..

Comment.—We have reviewed 82 cases of streptococcic empyema, in 17 of which treatment was by aspiration, in 27 by intercostal drainage and in 34 by rib resection drainage. In 4 additional cases treatment by the last method was ultimately considered unsuccessful. For each method employed some failures were presented: Aspiration alone failed in 35 per cent of the cases in which it was employed, intercostal drainage in 7 per cent and rib resection drainage in 11 per cent. The mortality was highest (50 per cent) in the patients subjected to aspiration and lowest (8 per cent) in those treated by rib resection drainage. In those treated by intercostal drainage it was 20 per cent. As in the cases of pneumococcic empyema, the mortality was directly proportional to the number and severity of complications and was not attributable to the empyema per se, as shown in the accompanying tabulation:

	Percentage
All complications	32
Total mortality	27
Mortality in cases of complicated empyema	65
Mortality in cases of uncomplicated empyema	9

The average period of hospitalization for the surviving patients was twenty-four days for those treated by aspiration, thirty days for those subjected to intercostal drainage and thirty days for those treated by rib resection drainage. Considering these figures, we note that the method of choice is either closed intercostal drainage or rib resection drainage.

Since streptococcic empyema occurs early in the course of the pneumonic process, rib resection drainage must be deferred as long as possible. A closed intercostal subaqueous drainage therefore appears to

be the most logical method—at least during the formative stages of the pneumonia. If the work of Graham and Bell is applicable to pneumococcic empyema it most certainly is applicable to the streptococcic empyema. Intercostal drainage can easily be performed at the patient's bedside. The egress of pus can readily be controlled by a stopcock. Our objection to repeated aspiration is that the chance of the development of empyema necessitatis or of subcutaneous infection is greatly enhanced with repeated aspirations of the pleural content. In addition, the removal of the fluid from the pleural cavity (by aspiration) is accomplished relatively rapidly. A closed intercostal drainage can be instituted early and regulated to remove the fluid slowly and continuously. In the presence of a ruptured lung it will also act in such a manner as continuously to deflate the pleural cavity. It is frequently stated that the objection to this method of drainage is that the opening in the wall of the chest soon becomes large enough to permit the entrance of air into the pleural cavity. Generally leakage about the tube does not occur before a week or ten days. By that time the acute pneumonic process has subsided or is subsiding. However, in the occasional case leakage will occur before that time. In any event, we have taken precautionary measures against leakage in all cases of intercostal drainage by using a collodion, rubber cement or liquid adhesive dressing about the drainage tube at its entrance into the thoracic wall. Since the pus in streptococcic empyema is relatively thin until late in the course of the disease, we have found that the intercostal tube affords adequate means of drainage. In several instances in which closed intercostal subaqueous drainage was instituted during the acute pneumonic process and while the pus was still thin we found that this sufficed to evacuate completely the pleural cavity and permit complete reexpansion of the lung and cure of the empyema.

STAPHYLOCOCCIC EMPYEMA

Charts 7, 8 and 9 represent the results of the various procedures employed at this institution in the drainage of staphylococcic empyema. In 8 of the 33 cases recorded in these charts the diagnosis of empyema was made before the tenth day of illness, and in 14 it was made between the eleventh and the fourteenth day. In the remaining 11 cases the diagnosis was made after the fourteenth day of illness. In 4 of the last group of cases the patient was admitted with a known history of empyema of over one month's duration. From our observations, therefore, it appears that staphylococcic empyema may occur at almost any time during or after the acute pneumonic process. The tendency, however, appears to be for it to occur somewhat more commonly after the pneumonic process begins to undergo resolution.

Chart 7 represents 9 cases in which staphylococcic empyema was treated by repeated aspiration. Two of these were cases of uncomplicated and 7 of complicated empyema. It will be noted that the mortality in these cases was 100 per cent. There was but 1 case in which the patient survived long enough to permit some other form of drainage. This patient was an extremely sick infant, 5 weeks of age, who was admitted to the hospital on the third day of illness with pneumonia, a lung abscess and empyema. Thoracentesis was begun soon after the patient's admission. On the fourteenth day of illness suppurative pericarditis developed, and on the twenty-third day the patient died. There were no cases in which this method of treatment could be

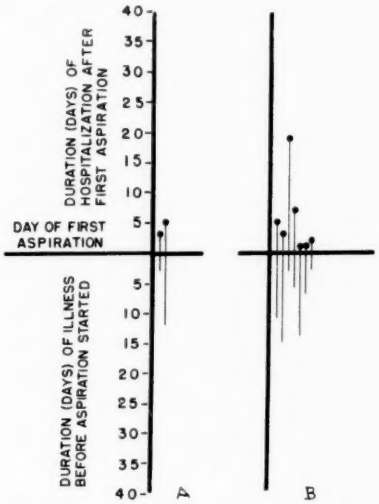

Chart 7.—Nine cases in which staphylococcic empyema was treated by aspiration. See legend to chart 2.

termed "unsuccessful," since all patients in the series died. The complications were as follows:

Complication	No.	Mortality
Pneumonia, lung abscess and pericarditis	1	1
Lung abscess and pericarditis	1	1
Lung abscess and pneumonia	1	1
Pericarditis and pneumonia	1	1
Lung abscess	3	3

Chart 8 represents 14 cases in which staphylococcic empyema was treated by intercostal drainage. Of these cases 8 were of uncomplicated and 6 of complicated empyema. The total mortality in the 14

cases was 4, or 29 per cent. There were no fatalities from uncomplicated empyema, whereas from complicated empyema there were 4 deaths, a mortality of 67 per cent. In addition, there were 3 patients with uncomplicated empyema who were treated by intercostal drainage and failed to respond to this method of treatment. These 3 patients were later subjected to rib resection drainage. The total mortality on the basis of the 17 cases was therefore 24 per cent. The mortality from uncomplicated and that from complicated empyema remain unchanged. The average time at which drainage was instituted in these cases was the fourteenth day of illness. The average period of postoperative hospitalization for patients with uncomplicated empyema was twenty-seven days, and that for the 2 patients surviving complicated empyema was

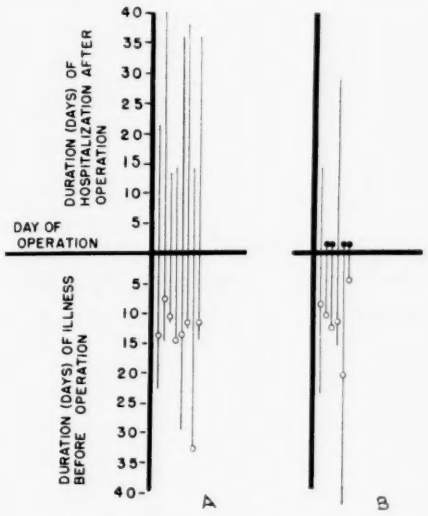

Chart 8.—Fourteen cases in which staphylococcic empyema was treated by intercostal drainage. See legend to chart 2.

twenty-two days. There were 4 patients with uncomplicated empyema who required two weeks or less of postoperative hospitalization and 1 with complicated empyema who required a similar period. No patient required more than six weeks of postoperative hospitalization. It is of interest to point out that the deaths of all 4 patients with complicated empyema occurred within twenty-four hours after surgical intervention. The complications in the 6 cases were as follows:

Complication	No.	Mortality
Lung abscess	3	2
Ruptured lung abscess	1	1
Pleurobronchial fistula	1	..
Lung abscess and bilateral bronchopneumonia	1	1

Chart 9 correlates the mortality with the age of the patient and the period of hospitalization in 10 cases in which staphylococcic empyema was treated by rib resection drainage. In this group of cases there were 8 of uncomplicated and 2 of complicated empyema. In addition, in 2 cases in which uncomplicated empyema had previously been treated by intercostal drainage rib resection drainage was ultimately considered unsuccessful. There were no fatalities either in the cases of complicated or in those of uncomplicated empyema in which this method was

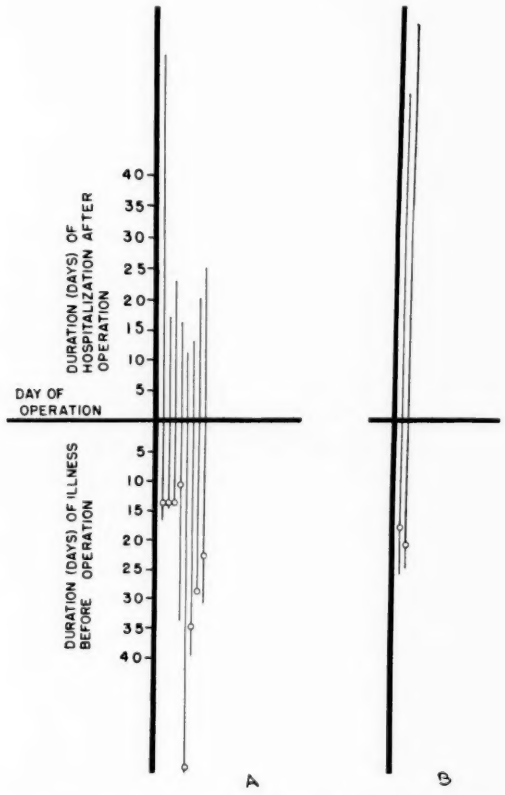

Chart 9.—Ten cases in which staphylococcic empyema was treated by rib resection drainage. See legend to chart 2.

used. On the average, drainage was instituted for uncomplicated empyema on the twenty-sixth day of illness and for the complicated disease on the twentieth day. One patient with uncomplicated empyema was admitted to the hospital on the sixty-second day of illness, and drainage was instituted two days later.

There were 2 patients with uncomplicated empyema who required less than two weeks of postoperative hospitalization and 1 who required

more than six weeks. One of the patients who had a previous intercostal drainage required twenty-five days of hospitalization after rib resection drainage was instituted. Both patients who had complications required more than six weeks of postoperative hospitalization and secondary operations for the underlying complication, one of which was a lung abscess and the other a subphrenic abscess.

Comment.—In the foregoing section, we have reviewed 35 cases of staphylococcic empyema, in 9 of which treatment was by aspiration, in 14 by intercostal drainage and in 12 by rib resection drainage. In 2 of the cases treatment by rib resection drainage was finally considered a failure. No patient treated by aspiration survived long enough for that method to be considered a failure. Intercostal drainage failed in 3 cases (18 per cent) and rib resection drainage in 2 (17 per cent). Mortality was 100 per cent in the cases in which treatment was by aspiration, and 24 per cent in those in which it was by intercostal drainage; there were no fatalities in those cases in which treatment was by rib resection drainage. The mortality, as shown in the accompanying tabulation, appeared to be directly proportional to the inadequacy of drainage as well as to the number and severity of complications.

	Percentage
All complications	43
Total mortality	37
Mortality in cases of complicated empyema	74
Mortality in cases of uncomplicated empyema	10

It appears therefore that procrastination in treatment of staphylococcic empyema invites complications and increases the mortality. The only method which has given satisfactory results is rib resection drainage. Aside from the fact that it yields poor results, repeated aspiration in cases of staphylococcic empyema should be avoided because of the tendency of the staphylococcus to spread.

Staphylococcic empyema is believed by some to be due to the rupture of a subpleural abscess. We have observed this so infrequently that we cannot subscribe to this point of view in all cases. We do believe, however, that it occurs more often in staphlococcic empyema than in the other forms. Rib resection drainage during the formative stages of the disease must be avoided here as with streptococcic and pneumococcic empyema. An air-tight, closed intercostal drainage during this period will relieve the dyspnea and the toxemia and often will save the life of the patient. When the patient's condition has become more favorable rib resection drainage may be instituted. We are of the same opinion as Neuhof and Berck [12] that "the minor procedure of closed

12. Neuhof, H., and Berck, M.: Staphylococcic Empyema and Pyopneumothorax: Pathogenesis, Pathology, Symptoms and Treatment, Arch. Surg. **30**:543 (March) 1935.

drainage adequately cares for the acute pathologic process in the pleura, although later revision of the wound is not infrequently required for cure."

The complications in staphylococcic empyema assume even greater importance than they do in pneumococcic and streptococcic empyema.

EMPYEMA DUE TO MORE THAN ONE ORGANISM

In this series there were 28 cases in which more than one organism was present in the pleural fluid (chart 10). In 13 cases there were pneumococci and streptococci; in 5 cases there were pneumococci and staphylococci; in 3 cases there were pneumococci, streptococci and staphylococci, and in 7 cases the micro-organisms were streptococci and staphylococci. Rib resection drainage failed in 1 case in each of the last two groups. The first case was that of a child with a perforated lung abscess, pleurobronchial fistula and empyema in which the lung failed to expand after ninety days of postoperative hospitalization. The second case was that of a child with a large residual pneumothorax who was removed from the hospital against advice on the eighty-fourth postoperative day. It is of interest to point out that this patient was previously treated by intercostal drainage for twenty-seven days before rib resection drainage was instituted. In addition, it may be pointed out that in the second of the 2 cases in which intercostal drainage failed and the patient was later subjected to rib resection drainage, multiple pockets of empyema developed which required three thoracotomies and seventy-two days of postoperative hospitalization.

In the 26 cases recorded in chart 10 it will be seen that there were 5 fatalities, a mortality of 19 per cent. In the 5 cases in which treatment was by aspiration there were 4 (80 per cent) fatalities; in the 4 cases in which treatment was by intercostal drainage there were no deaths, and in the 17 cases in which treatment was by rib resection drainage there was 1 death, a mortality of 6 per cent. This patient was a 13 year old child who was ill for over four months before admission to the hospital. There is reason to believe that the patient had empyema of at least three months' duration. She was admitted to the hospital in a moribund state and died within twenty-four hours after surgical intervention.

As in the previous cases, regardless of the method of treatment, the mortality was highest from complicated empyema. The 4 fatalities in the 5 cases in which treatment was by aspiration were in cases of complicated empyema, while the 1 patient who survived had no complications. The 4 patients treated by intercostal drainage had uncomplicated empyema. There were 3 patients with complicated empyema treated by rib resection drainage with no fatality and 14 with uncompli-

cated empyema with 1 fatality (previously described). The complications are given in table 2.

Comment.—Although our series of 28 cases of empyema due to more than one micro-organism is too small to allow us to draw any definite conclusions, certain observations may be recorded. The point of the greatest importance in these cases is that empyema from mixed organisms may occur at any time during the course of the acute pneumonic process and that the earlier it occurs the more serious is its

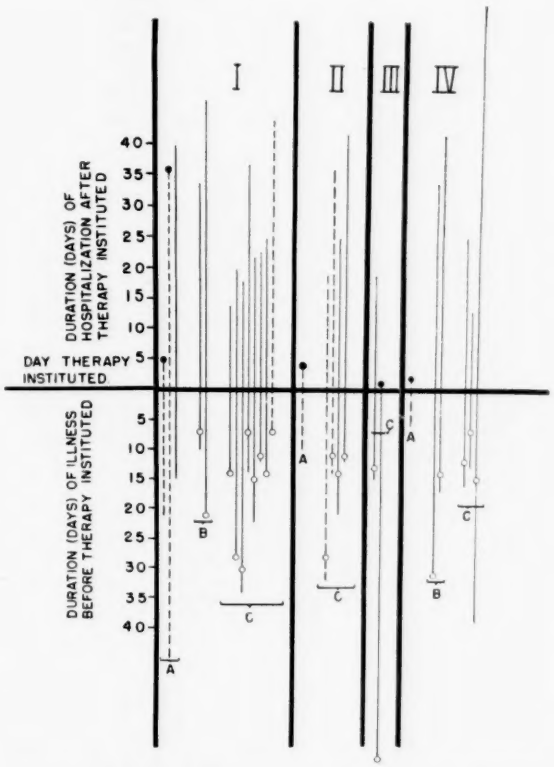

Chart 10.—Twenty-six cases of empyema due to more than one organism. *I* represents 13 cases of empyema due to pneumococci and streptococci; *II* represents 5 cases of empyema due to pneumococci and staphylococci; *III* represents 12 cases of empyema due to pneumococci, streptococci and staphylococci; *IV* represents 6 cases of empyema due to streptococci and staphylococci. The broken line indicates cases of complicated empyema; the solid line indicates cases of uncomplicated empyema. *A* denotes cases in which treatment was by aspiration; *B* denotes cases in which treatment was by intercostal drainage; *C* denotes cases in which treatment was by rib resection drainage.

outlook. Second, it may present any of the features shown by other acute nontuberculous empyemas. Third, a mixed infection may be due to the underlying or primary process, or it may be the result of the intro-

duction of organisms from without during aspiration in a case of empyema due to a single organism. Lastly, rib resection drainage should be instituted as soon as the pus becomes thick, the pneumonic process has subsided and the lung becomes adherent to the thoracic wall.

COMMENT

The *Quarterly Cumulative Index Medicus* for the ten year period between 1928 and 1937, inclusive, lists a yearly average of twenty-five references to empyema in infants and children. These references cover many phases of the subject. A discussion of the physical signs and roentgenographic findings in acute nontuberculous empyema is therefore readily available and need not detain one. Suffice it to say that in any case in which there are a history of recent pneumonitis, an

TABLE 2.—*Complications in Cases of Empyema Due to More Than One Organism*

Complication	Organisms	Number	Mortality
Bilateral bronchopneumonia	Streptococcus, staphylococcus	1	1
Pericarditis	Pneumococcus, streptococcus	1	1
	Pneumococcus, staphylococcus	1	1
Pleurobronchial fistula	Pneumococcus, streptococcus	1	..
	Pneumococcus, staphylococcus	1	..
Lung abscess	Pneumococcus, streptococcus	1	..
	Pneumococcus, staphylococcus	1	1

elevated temperature and flatness on percussion of the thorax the presumptive diagnosis is empyema. The final diagnosis rests on the aspiration of pus from the pleural cavity. In all cases of suspected empyema we wish to reemphasize the importance of a diagnostic puncture. The gross appearance of the exudate will usually tell the physician whether the fluid is thick or thin, purulent or serous. Microscopic examination will confirm the presence or absence of pus cells. Culture will tell which organism is responsible for the empyema and will determine the prognosis and treatment. Da Costa [13] aptly stated that

> while aspiration into the thoracic cavity is not entirely devoid of danger, the fatality rate of infants in whom the condition is undiagnosed and untreated is so much higher than it is among patients in whom needless punctures have been made for suspected empyema, that Osler's admonition to a young intern should be

13. Da Costa, J. C.: Modern Surgery, General and Operative, Philadelphia, W. B. Saunders Company, 1931.

profitably followed: "In any case of presumptive empyema, an exploring needle should be inserted in seven places seventy times before the possibility of empyema can be eliminated."

The diagnosis of empyema is not difficult in even the youngest subject, although it may be overlooked when it occurs during the acute phase of the pneumonic process. In our own cases empyema was noted at postmortem examination in several instances in which the child died apparently of pneumonia. Rienhoff and Davison,[14] in a study made at the Johns Hopkins Hospital of 80 patients under 2 years of age, noted that the diagnosis was not made until the time of necropsy in approximately 20 per cent of the cases. From our observations at the time of necropsy in similar cases we believe that even had the diagnosis been made in such cases no adequate treatment could have been instituted because of the poor condition of the patient. In every instance in which necropsy was performed on a patient with undiagnosed empyema there was an associated acute pneumonic process (unilateral or bilateral), which was further complicated by suppurative mediastinitis, pericarditis, lung abscess, peritonitis, meningitis or septicemia. The incidental finding of empyema does not imply that if the diagnosis had been made the patient's life would have been saved. Empyema is seldom a surgical emergency, and is still less often a surgical emergency during the acute phase of pneumonia. In fact, it has often been shown that in those instances in which some pus was aspirated from the chest the patient did well as long as drainage was not instituted during the acute pneumonic phase, whereas in those instances in which drainage was instituted as soon as the diagnosis was made the mortality was high. The management of empyema requires more than "just sticking a tube into the chest for drainage." It requires clinical judgment as well as skilful and judicious care which is not entirely surgical. In the early stages of the disease it is best treated by supportive measures and neglect of direct attention to the empyema itself.

An examination of the procedures advocated in the management of empyema from the time of Hippocrates,[15] who suggested watchful waiting, to that of Koster and his associates,[16] who recently suggested contralateral pneumothorax with surgical drainage of the pus, shows that all methods attempt to hasten the patient's recovery by stressing the

14. Rienhoff, W. F., Jr., and Davison, W. C.: Empyema in Infants Under Two Years of Age, Arch. Surg. **17**:676 (Oct.) 1928.

15. Hippocrates: The Genuine Works of Hippocrates, translated by F. Adams, London, Sydenham Society, 1849.

16. Koster, H.; Kasman, L. P., and Rosenblum, J.: A Suggested Method for More Rapidly Curing Empyema, Ann. Surg. **106**:992, 1937.

importance of one or more of the following phases: (1) evacuation of the pus, (2) sterilization of the pleural cavity, (3) reexpansion of the lung and obliteration of the pleural space and (4) restitution of the thorax to integrity. It should be stated that no empyema can be considered cured until all four objectives have been attained. The problem which confronts the physician is not one of immediate cure but of the greatest number of cures at the least expense of life and with the shortest period of debility. To this end the analysis of our cases will be used as a basis for our conclusions. We must confess at the very outset that the stage of the empyema, the age of the patient, the etiologic organism and any additional complications influenced our final choice of method and determined the prognosis in every case. Whenever possible the empyema should not be attacked surgically until other complications have been ruled out or, if present, have subsided or are controlled. Frequently such complications assume greater importance with respect to the life of the patient than does the empyema. The aim of the surgeon is to drain the pus of uncomplicated empyema as quickly and as adequately as the patient's condition will permit and to help restore the patient's health as soon as possible. Drainage may be accomplished by (1) aspiration, (2) intercostal drainage or (3) rib resection drainage—or by any modification thereof.

Aspiration is only a diagnostic or palliative treatment, although occasionally it may suffice to cure a localized pleural collection of pus. Repeated aspiration, however, in the presence of a large pleural effusion is neither sound surgically nor innocuous. Particularly with staphylococcic empyema must one be cautious. A subcutaneous abscess may readily be produced even when precautions are taken to prevent its occurrence. The resulting phlegmon of the thoracic wall starts deep and may not be recognized until the process has advanced a considerable distance. Aspiration to cure empyema was first introduced in 1844. Since that time it has been frequently revived as a method of treatment. Among the 76 patients treated by this method there were 38 deaths and 28 cases in which it was unsuccessful. Such statistical results do not, therefore, support the contention that aspiration is of much curative value in the treatment of empyema.

A closed intercostal drainage has many advantages over the aspiration method in that it requires but one entrance into the pleural cavity and can be so arranged that it functions as a continuous drainage system. The rapid or sudden release of pus which takes place during aspiration in cases of empyema in children may produce pulmonary edema and further decrease the vital capacity of that lung. This, too, may be obviated by a simple closed intercostal drainage. In the 88 cases of our series in which treatment was by intercostal drainage there were 11

deaths and 20 cases in which this method of drainage was a failure. These results are considerably better than those obtained by aspiration. This procedure, however, does not yield such results in all cases of empyema. The most striking and dramatic results of closed intercostal drainage were obtained in those cases in which the patient was acutely ill and in which there was cardiorespiratory embarrassment. The relief of some of the tension caused by the massive effusion was often striking and lasting, and indeed saved the life of more than one patient. If early surgical intervention is necessary, owing to the rapid reaccumulation of pus and interference with cardiorespiratory function, the simplest method must be chosen which will give the maximum and the longest relief, as well as permit continuous drainage. During the acute pneumonic phase, regardless of whether the etiologic organism is the streptococcus, the pneumococcus, the staphylococcus or a combination of several of these micro-organisms, such a method is the only one which can be employed with any degree of safety. The closed intercostal subaqueous, continuous, regulated drainage answers all the requirements. However, when there is delay in institution of drainage and when the pus has become thicker this method of drainage is usually inadequate.

Of all the methods proposed, rib resection drainage or some modification thereof appears to be the most serviceable in the treatment of empyema. Except in those cases in which the pus is thin or in which empyema is of very recent date, rib resection drainage ensures the best method of drainage with the least embarrassment to the patient. Among the 151 patients treated by this method there were 8 deaths and 12 cases in which the patient failed to respond satisfactorily. In cases of early empyema, especially the streptococcic form, rib resection drainage should be considered as contraindicated. The opening in the pleura after rib resection is usually of such size that it increases the collapse of the affected lung. Such collapse, particularly during active pneumonia, will decrease the vital capacity, increase the anoxemia and contribute to the patient's embarrassment. It may also cause asphyxial death. On the other hand, such an opening in the cases of pneumococcic empyema will afford ample opening for adequate drainage without embarrassment to the patient. Once the acute pneumonic process has subsided and the drainage instituted during that phase has proved inadequate, rib resection drainage should be instituted without further delay. In cases of streptococcic empyema it should be delayed until the pus becomes thick. In cases of pneumococcic empyema rib resection drainage may be instituted as soon as the patient's condition begins to improve. In cases of staphylococcic empyema it should be performed as soon as intercostal drainage has proved inadequate. In the case of empyema due to mixed organisms the course to be taken depends on the character

of the pus, the condition of the underlying lung and the characteristics of the predominating organism in the pleural exudate.

The foregoing method is particularly applicable in cases of uncomplicated empyema and in those of empyema complicated by a rupture of the visceral pleura. Of far greater importance to the life of a patient with empyema is the management of the postpneumonic complications associated with the empyema. In these cases we wish to reemphasize the fact that such complications are often of greater importance than the empyema itself and that therefore efforts must be made to minimize the gravity of these complications before the empyema is attacked. Heuer [17] stated:

> From my study of this series of cases [Johns Hopkins] it is clear that patients dying after operation for empyema showed at necropsy almost without exception some serious pathological condition in addition to the empyema. . . . The mortality . . . varied according to age, according to the type of infection and according to the kind and number of pathologic conditions present in addition to the empyema.

The number of deaths from empyema per se is negligible as compared with the tremendous mortality from complicated empyema. In the 70 cases of complicated empyema there was a mortality of 48 (69 per cent), whereas in the 185 cases of uncomplicated empyema mortality was 9 (5 per cent). It is of interest to note that with complicated empyema there were 31 patients (45 per cent) below 2 years of age, 26 (84 per cent) of whom died, whereas of the 39 patients with uncomplicated empyema below 2 years of age only 3 (8 per cent) died. It therefore appears that complications tend to occur more frequently in children before the age of 2 years than after that age.

The most common complications encountered were (1) pneumonia, (2) pleurobronchial fistula and (3) lung abscess. It is beyond the scope of this communication to discuss methods of treating these complications.

CONCLUSIONS

1. Empyema is rarely a surgical emergency, whereas its complications are frequently surgical emergencies.

2. The mortality from empyema is related not to the age of the patient but rather to the severity of the secondary complications.

3. Complications associated with empyema occur more readily in patients below 2 years of age than in those above that age.

4. Aspiration should be reserved for diagnosis and not for treatment.

5. Intercostal drainage should be reserved for palliative treatment and for those cases in which the pus is thin.

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17. Heuer, G. J.: Acute Empyema, J. Thoracic Surg. **1**:461, 1932.

6. Rib resection drainage should be instituted after the acute pneumonic process has subsided and the pus has become thick.

7. Staphylococcic empyema usually requires earlier intervention.

8. Such associated complications as a pleurobronchial fistula and a lung abscess should not be attacked at the time the pus is being drained unless they are readily accessible and the procedure would involve minimal surgical trauma.

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CYANOSIS FROM USE OF SULFANILAMIDE

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Cyanosis occurring during sulfanilamide therapy has been reported frequently.[1] It does not seem to depend on the age of the patient, the daily dosage or the length of time the drug is administered. The cyanosis usually is not accompanied by other untoward actions of the drug. In our experience it has occurred when sulfanilamide alone was given. It is reported to be more likely to occur when other drugs containing sulfates, particularly magnesium sulfate, are also given.[2] The cyanosis usually disappears soon after the withdrawal of the sulfanilamide, but it may not completely disappear for several days. It has been stated that cyanosis due to methemoglobinemia is usually only of a few days' duration while that due to sulfhemoglobinemia persists for a week or longer.[1c] Often on readministration of the drug cyanosis will not reappear. We have on occasion continued with sulfanilamide therapy after cyanosis has developed and have observed no harmful results. It is still a question whether this is a safe procedure, even though accompanied by frequent examination of the blood.

When cyanosis is present, the patient rarely experiences any discomfort from it, and the respirations are not accelerated. The giving of oxygen does not decrease the intensity of the cyanosis, nor does it shorten the period of its presence. In keeping with this clinical obser-

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From the Otho S. A. Sprague Memorial Institute and the Children's Memorial Hospital.

1. (*a*) Archer, H. E., and Discombe, G.: Sulfhemoglobinemia: Its Cause and Prevention, with Special Reference to Treatment with Sulfanilamide, Lancet **2**:432 (Aug. 21) 1937. (*b*) Colebrook, L., and Kenny, M.: Treatment of Puerperal Infections and Experimental Infections in Mice with Prontosil, ibid. **1**:1279 (June 6) 1936. (*c*) Paton, J. P. J., and Eaton, J. C.: Sulphemoglobinemia and Methemoglobinemia Following Administration of Para-Aminobenzenesulphonamide, ibid. **1**:1159 (May 15) 1937. (*d*) Frost, L. D. B.: Sulphemoglobinemia Following Antistreptococcal Chemotherapy, ibid. **1**:510 (Feb. 27) 1937. (*e*) Discombe, G.: Sulfhemoglobinemia Following Sulfanilamide Treatment, ibid. **1**:626 (March 13) 1937. (*f*) Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives: Clinical Observations on Their Use in the Treatment of Infections Due to Beta Hemolytic Streptococci, Arch. Surg. **34**:351 (Feb.) 1937.

2. Colebrook and Kenny.[1b] Paton and Eaton.[1c]

vation, it has been recently shown[3] that the decrease in the oxygen saturation of the arterial blood is not sufficient to cause the cyanosis. However, the cyanosis does improve when blood transfusions are given. During cyanosis the blood itself becomes much darker than normal. This change in color is commensurate with the degree of cyanosis, the blood even becoming dark brown when the cyanosis is marked. When the blood serum is allowed to separate, the serum is found to have a normal color. The change of color then occurs in the solid elements, probably being due to some pigmentary change in the red blood cells. When determinations of hemoglobin are made by the Sahli method, the readings may be high.

Spectroscopic examination of blood from patients who were receiving sulfanilamide has been reported by several observers.[1] When cyanosis was present, and even before its occurrence, bands of sulfhemoglobin and of methemoglobin have been noted.[1c] Because of these reports and because similar absorption bands have been described after the administration of drugs derived from sulfur, nitrobenzene or aniline or absorption of sulfides or nitrites from the bands, the cyanosis occurring during sulfanilamide therapy is usually now referred to as due to sulfhemoglobinemia or methemoglobinemia.

In a large proportion of children to whom we have given fairly large doses of sulfanilamide (usually based on the dosage of 1 Gm. per 20 pounds (9 Kg.) of body weight), some degree of cyanosis has occurred. Examination of the blood of many of these cyanotic children with a Zeiss hand spectroscope failed in each instance to reveal absorption bands other than those of oxyhemoglobin. No absorption bands were present with a maximum wavelength of 630 mm., which is the wavelength of sulfhemoglobin and methemoglobin. In 2 instances of marked cyanosis (1, case 7 in the table) samples of blood were also examined with the large spectroscope at the University of Chicago, with similar negative results.

Because cyanosis in patients treated with sulfanilamide has been attributed to the presence of methemoglobin and sulfhemoglobin and because of our own failure in the cases of cyanotic patients to find absorption bands for these substances with the spectroscope, we examined specimens of the blood of several of these patients in order to determine if inactive forms of hemoglobin were present.

The gasometric determination of the methemoglobin content was carried out as outlined by Van Slyke and Neill.[4] We determined the content of the active

3. King, F. H.; Leslie, A., and Byrne, G.: Oxygen Saturation of Arterial Blood in the Cyanosis from Sulfanilamide, J. A. M. A. **110**:2069 (June 18) 1938.

4. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

form of hemoglobin capable of binding oxygen and carbon monoxide by measuring the carbon monoxide–binding capacity of the blood. The total hemoglobin content was determined by the carbon monoxide–binding capacity after the addition of sodium hydrosulfite ($Na_2S_2O_4$), which changed methemoglobin into active reduced hemoglobin. Duplicate determinations made in 6 of the cases checked closely. With this method the difference between the total hemoglobin and the active

Results of Examination of the Blood of Nine Cyanotic Patients

Case No. and Age	Clinical Data	Cyanosis			Hemoglobin					
					Active		Total		Inactive	
		Onset	Termination	Date	Carbon Monoxide, Vol. %	Gm.	Carbon Monoxide, Vol. %	Gm.	Gm.	Percentage
1 10 yr.	Fracture; 40 grains daily 9/3 to 9/7, 60 grains daily 9/7 to 9/21	None	....	9/3	19.48 19.45	14.50 14.50	19.75	14.70	None	
2 11 yr.	Convalescent from tuberculosis; 30 grains daily 12/4 to 12/8, 45 grains daily 12/8 to 12/17	None	....	12/2	18.50 17.84	13.80 13.30	17.82	13.29	None	
3 18 mo.	Cervical adenitis; 15 grains daily 12/7 to 12/14	None	....	12/7	13.07	9.75	13.07	9.75	None	
4 10 yr.	Chorea; 45 grains daily 9/3 to 9/9, no cyanosis; 60 grains 9/9, cyanosis within 24 hours	9/10	9/13	9/2 9/10	15.60 19.20	11.64 14.30	15.55 19.20	11.60 14.00	None	
5 10 yr.	Pyuria; 45 grains daily 8/30 to 9/2, 20 grains daily 9/2 to 9/6, intermittently 9/12 to 10/5	9/5	9/10	9/7	17.18 16.70	12.80 12.40	15.87 16.70	11.70 12.40	None	
6 36 yr.	Streptococcus haemolyticus septicemia; 90 grains daily 9/19 to 10/1; also some drug given previously	9/13	10/9	9/27	10.35 10.35 10.35	7.72 7.72 7.72	12.02 12.07	8.97 9.00	1.25 1.28	13.9 14.2
7 30 mo.	Staphylococcus septicemia, acute purulent arthritis; 15 grains 11/5	11/6	11/7	11/6	11.20 11.20	8.30 8.30	14.57 13.95	10.87 10.41	2.57 2.11	23.6 20.3
8 7 yr.	Streptococcic meningitis, bilateral otitis media, mastoiditis; average dose 60 grains daily 12/25 to 1/29, 20 grains daily 1/29 to 2/1	12/27	1/1	.... 12/27 12/30 12/31	12.78 12.81 11.71 9.35	9.53 9.56 8.74 6.97	23.63 23.54 11.97	17.63 17.56 8.94	8.07 8.82 1.97	45.6 50.2 22.0
9 12 yr.	Hemolytic anemia following administration of 105 grains in 5 days, 1/23 to 1/28; jaundice 1/27	None	....	1/31	11.68	8.71	15.68	11.70	2.99	25.5

hemoglobin content indicates the amount of inactive hemoglobin, supposedly methemoglobin.

The results are given in the accompanying table. In cases 1, 2 and 3 the determinations were made before sulfanilamide was given. As no cyanosis developed, further determinations were not made. The figures in these 3 cases show only the close relationship of total and of active hemoglobin by the method employed with normal blood. In

cases 4 and 5 cyanosis was present. There was, however, no inactive hemoglobin, as the amount of active hemoglobin equaled the amount of total hemoglobin. In case 4 the blood was examined also before the sulfanilamide was given.

Cyanosis was also present in cases 6, 7 and 8. According to the methods employed, 1.25 to 8.82 Gm. of inactive hemoglobin was present. This is in contrast to the absence of inactive hemoglobin in the preceding 2 cases in which there was cyanosis. In case 8 a sample of blood was examined in another laboratory also, with the same results as ours. In addition, at the time when 8.82 Gm., or 45.6 per cent, of inactive hemoglobin was present, a spectroscopic examination of the same sample of blood was made with a large spectroscope, which revealed absence of all absorption bands except those of oxyhemoglobin. Because of our previous experience with cyanosis, administration of the drug was not stopped but was continued with the same dose after the cyanosis developed. The cyanosis disappeared while the drug was being administered and did not recur during the three subsequent weeks of medication. Coincidentally with the disappearance of the cyanosis the amount of inactive hemoglobin decreased.

In case 9 a hemolytic type of anemia developed during sulfanilamide therapy. There was no evident cyanosis at any time. Even in the absence of cyanosis the blood contained 2.99 Gm., or 25.5 per cent, of inactive hemoglobin.

From our data it is apparent that the cyanosis which occurs during sulfanilamide therapy is not dependent on the presence of appreciable amounts of inactive hemoglobin in the blood. The cyanosis occurred when no inactive hemoglobin was present as well as when there were small to large amounts. In case 9 in which there was 25.5 per cent of inactive hemoglobin, no cyanosis was evident. Spectroscopic examination of the blood of these cyanotic patients may indicate no sulfhemoglobin or methemoglobin although large amounts of inactive hemoglobin are present. The term "inactive hemoglobin" has been used to denote the amount of nonfunctional hemoglobin. Nonfunctional hemoglobin undergoes the change characteristic of methemoglobin by being reduced to hemoglobin on the addition of sodium hydrosulfite. But on spectroscopic examination no absorption bands characteristic of methemoglobin were seen.

Marshall and Walzl [5] studied 7 cases of cyanosis which occurred during sulfanilamide medication. They compared the oxygen-carrying capacity with the amount of total iron pigment of the blood in an effort to determine the amount of nonfunctional hemoglobin. In only

5. Marshall, E. K., and Walzl, E. M.: On the Cyanosis from Sulfanilamide, Bull. Johns Hopkins Hosp. **61**:140 (Aug.) 1937.

2 of their 7 cases was any inactive hemoglobin present. In only 1 of their cases were absorption bands of methemoglobin present on spectroscopic examination, (1 of the cases in which there was inactive hemoglobin). They concluded that cyanosis may not be due to nonfunctional iron pigment.

SUMMARY

From the available accumulated data it is evident that the cause and the mechanism of production of the cyanosis that so frequently occurs during sulfanilamide therapy are still not clear. While in some instances spectroscopic examination of the blood has revealed the presence of sulfhemoglobin and methemoglobin bands, in other instances it has given negative results. The cyanosis may be present in the presence or absence of nonfunctional hemoglobin. When nonfunctional hemoglobin is present, it has some, but not all, of the characteristics of methemoglobin. Further, the cyanosis does not seem to be dependent on the oxygen saturation of the arterial blood. Certainly, further studies of this problem are necessary for clarification.

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DENTAL CARIES AMONG ESKIMOS OF THE KUSKOKWIM AREA OF ALASKA

III. A DIETARY STUDY OF THREE ESKIMO SETTLEMENTS

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In the previous reports in this series details were given of clinical, bacteriologic and chemical studies relating to dental caries among Eskimos of the isolated Kuskokwim area of southwestern Alaska. Among other findings it appeared that the prevalence of caries is closely correlated with degree of contact with the white man and that the types of caries found in abundance, particularly among the less primitive natives, are essentially those which predominate among the young of other lands. The bacteriologic and chemical data, which confirmed previous findings among white peoples, may help to explain certain aspects of the mechanism of dental caries; yet they throw little light on the more fundamental question of the cause of the disease, that is, on the reasons which underlie the susceptibility of certain persons to caries and the freedom of others from it. Among the Eskimo subjects of this investigation, however, the simple fact that certain groups are strikingly more subject to caries than others suggests directly that the causes of the disease among them are inherent in the differences between such groups.

In all probability the conditions which include the causes of dental caries are dietary, as indicated broadly by the previous studies on

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This paper is Unit 10, Section IV, of "Dental Studies of the Eskimos of North America," directed by L. M. Waugh, D.D.S., Consultant Dentist, Office of Indian Affairs, and Dental Director (Reserve) of the United States Public Health Service.

primitive and isolated peoples mentioned earlier,[1] as well as by many other reports on the disease.[2] Hence, as part of this investigation, data were collected on the diets and the dietary habits of certain groups of Eskimos. Three communities were selected for this purpose, after examination of some of their natives had revealed that they presented a prevalence of dental caries ranging from extremely low to high and that they offered, nevertheless, comparatively uncomplicated conditions for investigation. Bethel, in contrast, was not used for this purpose, since its five traders and considerable white population seemed to introduce relatively forbidding complexities. The information sought about the three communities pertained not only to the qualitative and the quantitative composition of the diets but to the dietary habits of the natives, such as the manner of preparation of individual foods; for in relation to dental caries the possible immediate effects on the teeth of foods as they are eaten must be considered together with their effects as agents of nutrition. Such information was obtained through the cooperation of white residents of the three settlements who were thoroughly familiar with native conditions as a result of several years of close association with them, and was supplemented as far as possible by direct observation in the field. In addition, samples of many of the foods used by the natives at the three settlements were collected for analysis.

Samples of food collected in the field were brought to the laboratory at Bethel and were dried at about 100 C. for seven or eight hours; their water loss was recorded; they were sealed in bottles with paraffin and shipped to the laboratory in New York for analysis.

ANALYTIC METHODS

Water Content.—About 5 Gm. of the sample in finely divided form was redried in a weighing bottle at 96 to 98 C. for approximately forty hours. The total water loss was calculated as the total of the value thus obtained and that previously obtained at Bethel.

Ash.—Approximately 2 Gm. of dried sample was weighed in a platinum crucible and ashed in an electric muffle at 500 to 550 C. for twenty to forty hours. Ashing was completed over a free flame by treatment with a few drops of concentrated nitric acid at dull red heat. The treatment with nitric acid was repeated one to three times if necessary.

Calcium.—The ash was dissolved in 5 cc. of 0.25 normal hydrochloric acid by being warmed on a steam bath. After being cooled, the solution was transferred by pipet to a 10 cc. volumetric flask. The crucible was rinsed with two 2 cc. portions of 0.25 normal hydrochloric acid, and the solution was made up to the

1. Rosebury, T., and Waugh, L. M.: Dental Caries Among Eskimos of the Kuskokwim Area of Alaska: I. Clinical and Bacteriologic Findings, Am. J. Dis. Child. **57**:871 (April) 1939.

2. Rosebury, T., in Gordon, S. M.: Dental Science and Dental Art, Philadelphia, Lea & Febiger, 1938.

10 cc. mark with the same acid. After centrifugation, 4 cc. of the solution of ash was analyzed for calcium. Four cubic centimeters of a 4 per cent solution of ammonium oxalate and 2 drops of a 0.04 per cent solution of bromcresol purple were added to the solution of ash in a 15 cc. centrifuge tube with a conical bottom, and the mixture was adjusted to a light red color (p_H about 6) with dilute solutions of ammonium hydroxide (7, 0.7 and 0.3 per cent) and dilute hydrochloric acid (1 and 0.1 per cent). After standing in the refrigerator overnight, the tube was centrifuged, and after draining for five minutes over several layers of filter paper the precipitate was washed with acetone [3] and a 0.57 per cent solution of ammonium hydroxide. The washing was conducted as follows: The precipitate was first broken up with 0.5 cc. of acetone and mixed with 1.5 cc. of the solution of ammonium hydroxide, added so that the wall of the centrifuge tube was washed. An additional 1.5 cc. of ammonium hydroxide was then added, with minimal mixing but with precaution again to cover the wall of the centrifuge tube. Approximately 0.25 cc. of acetone was then added without mixing. After centrifuging, decanting and draining for five minutes, the washing was repeated once. The acetone was then allowed to evaporate spontaneously, and the precipitate was dissolved in 3 cc. of a two normal solution of sulfuric acid and titrated with a 0.005 normal solution of potassium permanganate.

Phosphorus.—Approximately 0.3 Gm. of dried sample was weighed in a small weighing bottle and transferred to a pyrex digestion tube (25 by 200 mm.) graduated at 50 cc. The bottle containing small amounts of untransferred residue was weighed, and the weight of the sample was calculated by difference. Ten cubic centimeters of a ten normal solution of sulfuric acid (with a silica chip to prevent bumping) was added, and the mixture was heated in a calcium chloride bath until most of the water had been driven off. Digestion was continued by heating the mixture on an electric hot plate, the tubes being kept at an angle of 45 to 60 degrees. During digestion, 5 drops of a 30 per cent solution of hydrogen peroxide was added at 10 minute intervals. Generally from 70 to 100 drops of hydrogen peroxide was used. Digestion was completed by heating the material to boiling over a microburner, adding 3 drops of hydrogen peroxide and boiling for one to two minutes. If the solution became discolored, the treatment with hydrogen peroxide was repeated. After the solution had been cooled, 20 cc. of water was added; the solution was then heated in a bath of boiling water for about three minutes and was finally brought to boiling over a microburner, during constant shaking. When cool, the solution was diluted to 50 cc. Ten cubic centimeters was added to a 50 cc. volumetric flask, and the phosphorus content was determined by the method of Fiske and Subbarow.[4] Molybdate II (ammonium molybdate dissolved in three normal sulfuric acid) was used for both the unknown and the standard solution. Three standards were prepared: 2, 5 and 10 cc., respectively, of a standard solution of potassium dihydrogen phosphate (1 cc. being equal to 0.1 mg. of phosphorus) in a volume of 100 cc. To balance the acid contained in the aliquot analyzed, ten normal sulfuric acid was added.

Nitrogen.—This was determined in the phosphorus digest as follows: Two cubic centimeters of the digest was transferred to a 50 cc. volumetric flask, to which were added 30 cc. of water, 0.78 cc. of a 1:1 dilution of sulfuric acid,

3. Krasnow, F.; Karshan, M., and Krejci, L. E.: J. Lab. & Clin. Med. **17:** 1148, 1932.

4. Fiske, C. N., and Subbarow, Y.: J. Biol. Chem. **66:**375, 1925.

12 cc. of Nessler's reagent (according to Koch and McMeekin[5]) and water to the 50 cc. mark. This was compared with a standard containing 3 to 5 cc. of a standard solution of ammonium sulfate (1 cc. equal to 0.1 mg. of nitrogen) in a 50 cc. volumetric flask, to which were added 30 cc. of water, 1 cc. of a 1:1 dilution of sulfuric acid, 12 cc. of Nessler's reagent and water to the 50 cc. mark.

Lipids.—Approximately 3 Gm. of dried food was transferred to an extraction thimble (Whatman, double thickness), which had been previously extracted in a Soxhlet extractor with ether for four hours. After being weighed, the material was extracted with ether in a Soxhlet extractor for sixteen hours and was then dried for about twelve hours at 96 to 98 C. The lipid content was calculated from the loss in weight.

Carbohydrate.—This was calculated by subtracting the ash, protein, lipid (on a wet basis) and water from 100.

THE THREE SETTLEMENTS

The settlements studied comprised an orphanage for native children and those of mixed race, conducted by the Moravian mission, and the native villages of Kepnuk and Eek.

The Moravian Orphanage.—This constitutes the village of Nunapitsinghak, which lies on a slough of the Kuskokwim River about 18 miles (29 kilometers) above Bethel. The other nearest settlement, Quithluk, a native village, is about 3 miles (4 kilometers) away; the orphans are largely isolated from both white and native contact from outside. At the time of examination there were 31 orphans, including 21 full blood Eskimos and 10 of mixed race. Eighteen of the full blood natives were examined without selection; they ranged in age from 9 to 22 years (average 15.3) and had lived at the orphanage for one to eleven years (average six and one-tenth years). Of the 18 orphans, 5, or 27.8 per cent, were free from caries. The average percentage of carious teeth was 10.0. The routine at the orphanage includes brushing the teeth twice a day, with baking soda as a dentifrice; most of the subjects had clean mouths. Dental treatment is provided at intervals by the Indian Service, and amalgam fillings to the extent of 0.78 filling per subject were in evidence. Information relating to diet was provided by Mrs. Mary L. York, the supervisor, in terms of total amounts of all foods used by the orphans during one year.

Kepnuk.—This town (also given on local maps as Kipnuk or Kaepnuk), said to be one of the most primitive native villages in Alaska, is situated near the coast of the Bering Sea, south of Etiolin Strait. It has only two white residents, the teacher in the government school for natives and his wife. Mr. C. Foster Jones, the teacher for four years, provided the dietary information. It is generally known that the natives are almost completely free from dental caries. Kepnuk was not visited during the expedition, but 9 of its natives were examined at Kokok, where they were encamped for summer fishing and where additional data on their food habits were obtained. The subjects ranged from 9 to 40 years in age (average 21.6); 7 (78.8 per cent) were free from caries, while the other 2 had collectively only 3 cavities, all small. The average percentage of carious teeth among the 9 was 1.2; there were no missing teeth and no fillings. As previously indicated, the mouths of this small group were representative of the whole primitive group studied clinically.

5. Koch, F. C., and McMeekin, T. L.: J. Am. Chem. Soc. **56**:2066, 1924.

Eek.—This is a native village situated on a river of the same name, which empties into the Kuskokwim River on its east bank, near the head of Kuskokwim Bay. The fishing camps of Eek, which were visited by this expedition, are located a few miles from the village, nearer the mouth of the Eek River. There are no white settlements nearby. The Eek natives intermingle somewhat with those of Apokak, a native village a few miles further south on the coast of the bay; but apparently they do not intermingle at all with the natives who migrate during the summer to the opposite bank of the Kuskokwim River from the villages on the coast of the Bering Sea, such as Kepnuk. They have a somewhat different culture from that of the Kepnuk natives, and it is said that they differ somewhat in physical characteristics. Eek has a resident white trader in addition to the nurse-teacher (community worker) at the government school for natives; these, with the husband of the latter, constitute the white population of the village. Mrs. Hanna Oman, community worker at Eek for six years, provided the dietary information, and samples of food were obtained from the natives. The mouths of 18 natives from Eek and of 2 from Apokak were examined, the subjects ranging in age from 6 to about 70 years (average 24.0); of these, 8 were free from caries (40 per cent). The average percentage of caries for the group was 18.1; individual values for percentage of carious teeth ranged as high as 66.7 per cent. All but 2 of the 14 subjects not more than 25 years old had caries, whereas the remaining 6, ranging upward from 36 years of age, were all free from caries. Only 3 teeth were missing among the group examined, and no fillings or other evidences of dentistry were present.

THE THREE DIETS

General Description.—The diet at Kepnuk is an example of a primitive regimen, subject to a minimum of white influence and associated with little dental caries. At Eek, although primitive characteristics somewhat different from those at Kepnuk are in large measure retained, the influence of the white man is more marked, and the incidence of dental caries is high among the children. At the orphanage, on the other hand, white influence is maximal, such that few of the native dietary characteristics remain; yet here the incidence of caries, although distinctly higher than at Kepnuk, is also distinctly lower than at Eek. The orphanage diet resembles more closely than either of the others the usual diet of Americans or Europeans; it also differs from the others in being more constant in composition and in quantity throughout the year. At the native villages the food supply depends on the resources of an uncontrolled environment and is subject to extreme variations both quantitatively and qualitatively. Details for the three settlements are given separately in the following account.

The Orphanage Diet.—Fish, Meat, Eggs: Salmon and other fish are used in quantity as staples, the salmon being dried and smoked, fresh (boiled), salted or home canned; the other fish is usually boiled while fresh. The orphans eat the heads, eyes, skin and roe of the fish and suck the bones clean. Neither meat nor oil of the seal or of other aquatic mammals is used at all. Meat is provided chiefly by reindeer, available during the winter months as dressed carcasses without

heads. About one third of the carcasses are canned at the orphanage. The remainder, with livers, hearts and tongues in addition to the red meat, is eaten roasted or steamed and as soup. Small animals, chiefly rabbits, with occasional muskrats, are also eaten, and a small amount of salt pork is used. The orphans like to chew the bones, especially those of reindeer, and to crack them and eat the marrow.

Occasional ducks and geese and a variable supply of ptarmigan, caught and brought in by the orphans, are eaten. The feet, heads, livers and gizzards of the fowl are used, as well as the meat. Waxed hen's eggs are available only by donation and are used for sick inmates; a small amount of commercial dried egg powder is used for cooking. Eggs of wild fowl also are eaten only in small and variable amounts.

Fats: Commercial fats, chiefly butter packed in brine and smaller amounts of corn oil (mazola) and hydrogenated cottonseed oil (scoco), compensate in part for the lack of seal oil. Cod liver oil is dispensed in small amount.

Milk: There is no fresh milk here or elsewhere in the Kuskokwim region. Irradiated evaporated milk is supplied at the orphanage in moderate quantity, and prepared malted milk is given, especially to the sick children.

Vegetables: Garden vegetables, both fresh and commercially canned, are supplied in moderate variety and amount. A truck garden at the orphanage yields mainly cabbage, eaten boiled or raw as cole slaw; turnips, chiefly eaten raw, and turnip greens, eaten boiled. In addition, there are smaller amounts of lettuce, radishes, Swiss chard and carrots, all eaten raw, the last for the most part while still small. Carrot tops are boiled in soup. The fresh vegetables are available beyond the summer only for about two weeks after the freeze-up in late October or early November. Thereafter canned vegetables are used, chiefly spinach, with smaller amounts of tomatoes and other kinds. Potatoes are used in moderate amount, as well as dried bayo beans, lima beans and split peas.

Fruits: The wild native berries are most prominent, particularly the small salmonberries, which grow close to the ground and appear during the early summer, and the blueberries, during midsummer and late summer. Cranberries are available in smaller quantities during the early fall. The berries are eaten raw directly off the bush and also are picked and served at the orphanage with sugar. Some of the berry crop is used for jams, and a marmalade is prepared from wild rhubarb. Other fresh fruits are available in smaller amounts: apples, oranges and bananas, all imported, the first especially being served occasionally throughout the winter. Small amounts of canned apricots, peaches and mandarin oranges are also available, as well as moderate quantities of dried apples, white figs, prunes and raisins. The total annual amount of fruit is not large. It may be noted that constipation is said to be general among the orphans.

Cereal Products: Bread and rolls, baked at the orphanage with half white and half whole wheat flour, are served in large quantity. Few cakes or pies are baked, but biscuits, chiefly pilot bread or ship biscuit, are used in moderate amounts; pancakes (griddlecakes, distinct from the native variety) are rarely eaten. Sweet crackers are made available occasionally by donation. Cereal flakes or similar dried breakfast cereals are not used, but oatmeal, farina and corn meal are served for breakfast each morning; corn starch and rice are used for puddings, and rice and barley are eaten in soups. A moderate amount of macaroni is used.

Sugar, Candy: Both white and brown sugar are used in moderate quantity, in cocoa and weak tea, on berries and in jams and in frequent puddings and occasional gelatin desserts. Sugar sirup is served occasionally on bread or hot

rolls. A small amount of candy, chiefly hard sugar candy, chewing gum and, less commonly, chocolate or peanut bars, is given to the children after supper about four times each week.

The Kepnuk Diet.—Fish: From the beginning of the salmon run in early spring at least to early fall, salmon is the staple food. Some is boiled; some is air dried without being smoked; some is smoked over burning driftwood after preliminary air drying, and occasionally some is salted in weak brine. In addition, fish heads, some whole fish and some of the eggs are buried in holes dug in the glacial subsoil of the summer camps, covered and left for two weeks or longer; they are then eaten, perhaps only if other food is scarce. These preparations *(tipmuk* or *t'pa),* as collected for analysis, were translucent and gelatinous, with a potent odor, rancid rather than putrid. Both the heads and the eggs of salmon are also eaten, fresh and boiled; some of the eggs are dried and smoked or used in *agutak* (to be described). The entrails are probably not generally used as food, except in periods of great deprivation; the bones likewise, although sucked or chewed clean, are themselves probably not eaten. The whole summer catch of salmon, including dried fish, has usually been consumed by these people by the time they return from their summer camps to Kepnuk in the early fall.

Among other fish, the so-called needlefish is particularly prominent. This is a tiny fish, up to about 2 inches (5 cm.) long, with rows of spines on the back and sides. During six or seven months of the winter it may constitute the bulk of the Kepnuk diet. For the most part it is eaten raw and whole, even alive—bones, entrails and all—dipped in seal oil and with little chewing. Needlefish may be consumed in enormous quantities. It is said that two men may eat a bucketful at one sitting. Sometimes they are boiled to make a muddy soup, but, again, the whole fish and all the sediment are eaten. Another fish important numerically is the fresh water blackfish, weighing up to 1 pound (0.5 Kg.), caught during the early winter. This may be the chief food during the interval of its availability. These fish are eaten mainly boiled, perhaps sometimes raw or salted. Other fish eaten in smaller amounts include tomcod and smelt, caught during the fall and eaten dried or boiled, probably sometimes whole, and a few herring, in spring, and whitefish, in summer.

Meat: Seal, walrus and beluga, numerically important in the order named, are most common. These are obtained chiefly during April, May and June; the Kepnuk people do not get seal in winter. The red meat of all three is eaten boiled, chiefly after being dried, but some of it is cooked while fresh. The thick skin of these animals, particularly of the walrus, with its layer of blubber, is cut into slabs like bacon and eaten after little boiling. The flippers are esteemed as a delicacy, and the gastric contents of the walrus, consisting of clams and mussels, are often eaten. The bones are chewed, and their marrow is sucked out. Other mammals are not abundant at Kepnuk. A few reindeer may be obtained and rabbits are sometimes plentiful. In addition, mink, otter and muskrats may be used. Of all these animals the red meat chiefly is eaten; but it is said generally of the natives that they waste nothing; all of the animal either is eaten by themselves or by their dogs or is used for other purposes, such as to make skin parkas or kyaks.

Fowl: Geese, the largest and commonest of available fowl, are a prominent item of the summer diet, especially in June. They may be eaten in quantity, usually boiled; their eggs likewise are eaten either boiled or raw. Many other birds are eaten: in the summer, crane, swans and ducks; in winter, ptarmigan, owls and even gulls. All are usually boiled.

Fats: Aside from the fat which forms a large proportion of such foods as salmon and geese and which is not separated from the fish or meat, the oils of seal, walrus and beluga, especially the first, are a noteworthy part of the Kepnuk diet. Seal blubber is often eaten fresh and raw and is said to be esteemed as a delicacy. In addition, both seal oil and walrus oil are rendered crudely, the blubber being stuffed into sealskin pokes, which are allowed to lie on the ground or are buried, sometimes for several months. Some of the oil, particularly that of the walrus, is eaten by itself. Most of it is used by dipping the fish or other foods into it. A little of it is used for frying pancakes (to be described), the only frying indulged in by the Kepnuk natives.

Some of the oil is also used for *agutak*, a variable mixture of seal oil, blueberries or salmonberries, salmon eggs and perhaps other ingredients, such as mosses. In the winter this mixture is further admixed with snow. It is evidently a delicacy rather than a staple food.

Cod liver oil is distributed by the teacher among the children and the tuberculous adults during the school year.

Plant Foods: Berries are available in variety and amount similar to those at the orphanage. They are eaten directly off the bush or used in *agutak*. Some are preserved by being dried for making *agutak* in winter. A few roots and greens, including a root, said to be esteemed, which grows on the borders of brackish lakes and a form of wild rhubarb, are also eaten in variable quantity, probably never large.

White Man's Foods: Some of the Bethel traders make occasional stops at Kepnuk or at the summer camps, and thus a small amount of white man's food enters the Kepnuk diet. Tea, by far the most prominent item, is used in quantity, usually without sugar, as often as six times a day, at and between meals. Salt is used for pickling rather than for flavoring food. Flour is available in only small amounts and is probably used only by certain families, who make pancakes from a batter of flour and water, perhaps with baking powder, which is fried in seal oil, one to a large pan. Sugar is occasionally used with berries, in *agutak* or, rarely, in tea. Some natives use sugar and flour only to make a sort of beer.

Milk: Except for human milk, this is used by these people virtually not at all, but mothers uniformly nurse their children for prolonged periods, usually for at least three or four years and sometimes up to adolescence.

Tobacco: The practice of chewing is widespread and of dietary interest, since the tobacco is commonly mixed with the ash of a shelf fungus which grows on birches. This mixture is chewed and held in the mouth for long periods and may be stored and passed from mouth to mouth indefinitely. This practice recalls the observations of Pickerill [6] on the salivary stimulants used by primitive Maoris and other aboriginal peoples. The use of this fungus is also interesting as a probable source of calcium in the diet, as will be noted.

The Eek Diet.—Fish: Salmon, treated as at Kepnuk, is again important, but at Eek dried fish is a staple food throughout the year. The people of Eek do not get needlefish. Pike is caught in the early spring, and blackfish is available during the winter and may be used in enormous quantities (as many as thirty fish, each about 6 inches (15 cm.) long, are said not to be excessive for a man at one meal). Whitefish of several kinds are available during about one month in the fall.

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6. Pickerill, H. P.: The Prevention of Dental Caries and Oral Sepsis, ed. 3, New York, Paul B. Hoeber, 1924.

Cheet, a variety of catfish, are caught in the early spring; they are not important numerically, but have an extremely large liver, which is regarded by the natives as a delicacy.

Meat, Eggs: Seal is available, particularly during the spring break-up. Most of it is eaten boiled while fresh, but any great excess is dried. The liver, brain, lining of the stomach and perhaps other organs are eaten, but the bones are said to be thrown back into the river by ritual, to insure a supply of seal for the following year. Walrus and whales other than beluga are rare at Eek. Several beluga are usually obtained in the fall; they are treated like seal.

Among land animals reindeer, now herded under government protection, are most important. In addition to the meat, eaten fresh with little boiling, most of the organs other than the intestines are eaten; the bones are chewed and cracked, and the marrow is sucked out. Other large animals, such as the brown and the black bear, are eaten if obtained, but are rare. Small animals include the same varieties as at Kepnuk. With respect to fowl, likewise, Eek and Kepnuk appear to be similar, but at Eek the eggs of wild fowl are usually boiled hard.

Fats: Seal oil is again most important, being crudely rendered, as at Kepnuk, and used generally for the same purposes. The oils of beluga and of any walrus that may be caught are rendered and used in the same way. The natives of Eek, however, do not eat the fresh blubber of any of these animals as a rule, although the children like to chew pieces of seal or walrus skin. These people also prepare reindeer tallow; they render it, on the stove or in the oven, more carefully than seal oil, under white guidance. Reindeer tallow is used mainly for *agutak*, but it replaces seal oil for all purposes when the latter is gone. In addition, some commercial fats are used, particularly in summer: beef tallow, vegetable fats and a little lard. These people also receive cod liver oil from the teacher.

Plant Foods: A number of native vegetable foods are available, although again the aggregate quantity used is small. A food known as mouse nuts, available during about one month in the fall, appears to consist of the roots of certain grasses, which are collected first by field mice and are brought in from the mouse holes by the Eek children, who scrape off the outer layer and eat them raw. Several wild greens, the ends of reeds, the roots of grasses and the leaves of wild rhubarb, all obtained in the spring, are cooked and eaten with seal oil or other fat. A moss is eaten cooked with meats and probably also raw in *agutak*. Berries are again quantitatively most important among these foods, including, in addition to the varieties at the other communities, blackberries and a few thimbleberries, the latter a small, thorny variety of raspberry. Some of the berries are preserved by being packed in buckets or barrels, buried in the ground until fall or winter, under which conditions they are said to keep well.

White Man's Foods: Flour, sugar and tea, quantitatively in the order named, are all used in considerable amounts. The flour is used not only for pancakes, as at Kepnuk, but for bread, which is usually prepared with baking powder rather than with yeast and is baked in ovens in pans lined with seal oil. Sugar is used generously in tea, which is taken about four times a day, and is also mixed with *agutak* or eaten directly with pilot bread, the last especially by the children. Pilot bread is said to be popular among the children, whose lunch during the school year regularly consists of these biscuits eaten with sugar and followed by tea. Candy is available at Eek, but seems to be used only in small amounts. Rice, mainly or entirely polished, is popular; it is boiled with meats, particularly reindeer, ptarmigan and rabbit. Beans, including dried lima beans, bayo beans and white beans, are available, but not popular. Rolled oats, recently introduced, are occa-

sionally cooked as a gruel by some families. Other cereals are used little or not at all.

Milk: This is available only in canned form, and little or none is used, but, as at Kepnuk, children are breast fed for long periods.

QUANTITATIVE AND ANALYTIC DATA

The basic quantitative data are given in table 1 as the amounts of individual foods consumed at the three settlements, estimated in pounds

TABLE 1.—*Estimated Consumption of Foods at Eek, Kepnuk and the Moravian Orphanage* *

Food	Eek	Kepnuk	Orphanage
Salmon, dried	250	80	16.1
Salmon, fresh	90	90	90.0
Salmon, canned	...	...	25.8
Salmon, salt	...	...	9.7
Salmon, eggs	20	8	....
Tipmuk	10	5	....
Blackfish	100	100	....
Needlefish	...	400	....
Other fish	30	30	50.0
Seal, walrus, beluga	90	150	... .
Reindeer	75	10	105.0
Other animals	40	60	15.0
Salt pork	...	...	3.2
Livers, other organs	45	50	15.0
Birds	20	30	10.0
Eggs	10	20	2.0
Seal oil, etc.	25	50	....
Reindeer tallow	10	...	1.6
Commercial fats	3	...	1.6
Butter	...	...	6.5
Cod liver oil	3	3	1.3
Evaporated milk	...	...	98.4
Malted milk	...	...	10.0
Raw lettuce	...	...	5.0
Raw radishes	...	...	0.3
Raw carrots	...	...	0.3
Raw Swiss chard	...	...	2.0
Raw cabbage	...	...	6.0
Raw turnips	...	...	10.0
Raw native roots	2	2	....
Cooked potatoes	...	...	14.0
Cooked cabbage	...	...	6.0
Cooked tomatoes	...	...	1.0
Cooked turnips	...	...	2.0
Cooked turnip greens	...	...	10.0
Cooked spinach	..	..	2.0
Cooked carrot tops	..	..	0.3
Cooked onions (dried)	..	..	0.1
Cooked native roots	3	3	...
Cooked native greens	5	5	...
Other cooked vegetables	..	..	1.0
Dried bayo beans	0.5	..	6.5
Dried lima beans	..	..	5.0
Dried split peas	..	..	3.3
Fresh berries	80	80	80.0
Fresh oranges	..	..	6.7
Fresh apples	..	..	8.0
Fresh bananas	..	..	2.8
Canned apricots, peaches	..	..	1.6
Jams	..	..	6.0
Dried apples	..	..	1.6
Dried figs	..	..	1.6
Dried prunes	..	..	3.2
Dried raisins	..	..	3.2
Rice	5	..	8.0
Barley	..	..	6.5
Oatmeal, corn meal, farina	..	..	60.0
Bread	35	..	250.0
Rolls	..	..	12.0
Pancakes (seal oil)	75	10	....
Pilot bread	10	..	4.2
Graham crackers	..	..	2.0
Macaroni	..	..	6.5
Sugar, white	30	..	7.0
Sugar, brown	..	..	12.9
Sirup	..	..	0.5
Candy	2	..	5.0
Agutak	4	4	...
Gelatin	..	..	0.2
Cocoa	..	..	3.0

* Values are given as pounds per person per year.

per person on an annual basis. The data pertaining to the orphanage were derived by simple calculation from the quantities provided by Mrs. York, most of them being given as an annual total for the whole group of inmates. These data may be regarded as accurate within narrower limits than those for the other two settlements. The values for Eek and Kepnuk are estimated from more general information, including the relative preponderance of individual foods, the fraction of the year during which they are available and the amounts likely to be consumed during a single meal. This procedure, while admittedly subject to undetermined errors, yields a pattern which in all probability is included within the extremely broad range of variability of the actual

conditions. It permits no precise measurement of the significance of differences, of course, and indicates that presumptive significance can be attached only to large differences. In several instances, because the data justified no other procedure clearly, the values for individual foods at two or at all of the settlements have been set down at the same level.

Some of the differences that appear in table 1 and their factual basis are worth examining at this point. The values for both fish and meat, in aggregate, were adjusted to somewhat higher levels at Kepnuk than at Eek, both because such values are consistent with the individual data and because the Kepnuk diet contains a much smaller proportion of white man's food, which is of high caloric value. Among individual items in these categories, that for reindeer at Eek, provided from a government report prepared by Mrs. Oman, served as a basis helpful in adjustment of the other values. The values for livers and organs at Eek and Kepnuk are roughly proportional to the amount of animal food eaten, with the value for the orphanage somewhat lower in proportion, as is consistent with the available information. The rather low value for cod liver oil for the orphanage is based on the available total of 5 gallons (19 liters) per year distributed among 31 persons and does not agree with the stated dose of a dessertspoonful daily for eight months, which would involve a much higher value. At Eek and Kepnuk the values given are based conservatively on a daily dose of 1 teaspoonful (estimated as 2 fluiddrachms [7 cc.]) during six months.

The other differences that require comment fall in the categories of white man's food. The values for bread and rolls at the orphanage are based on the annual consumption of flour and those for pilot bread and other crackers on the annual purchases. At Eek the values for bread and pancakes were distributed on the basis of the estimate of 60 pounds (27 Kg.) of flour consumed on the average per person per year. The value for pilot bread at Eek is based on an estimated half a biscuit per person per day (18 biscuits to the pound [0.5 Kg.]) and is probably a conservative figure. The value for pancakes at Kepnuk is arbitrary and is probably maximal.

The value for sugar at Eek was estimated on the basis of Mrs. Oman's statement that the natives used about 4 heaping teaspoonfuls (each about ⅓ ounce; 9 Gm.) per day per person, which, consistent with the general picture given, totals higher than the combined values for white and brown sugar at the orphanage, as derived from the total annual purchase. The value for candy at Eek is derived directly from Mrs. Oman's statement that she had given out 50 pounds (23 Kg.) to 50 children during a year and that they had obtained about as much again at the store. This yields a total which is small on an absolute

basis and is distinctly smaller than the moderate value for the orphanage. Sugar and candy, among white man's foods other than flour, are not listed for Kepnuk, since, although some of these foods

TABLE 2.—*Original Analyses of Foods of Alaskan Eskimos* *

Food	Source	Water	Ash	Calcium	Phosphorus	Protein	Fat	Carbohydrate
Salmon, dried	Pepok	27.74	3.67	0.130	0.714	68.6	1.4	0
Salmon, dried smoked	Orphanage	11.29	2.82	0.032	0.580	46.0	38.4	1.4
Salmon, dried smoked	Eek	18.00	2.50	0.034	0.585	51.7	24.0	3.8
Salmon, dried smoked	Kokok	47.91	6.75	0.020	0.253	25.7	17.4	2.2
Salmon, dried smoked	Kokok	33.60	8.25	0.021	0.453	46.3	10.5	1.4
Salmon, dried, average†				0.047	0.517	47.7	18.5	1.8
Salmon, fresh	Kokok	76.34	0.77	0.011	0.182	20.8	2.1	0.05
Salmon, fresh	Orphanage	73.73	1.35	0.069	0.236	21.1	2.9	0.9
Salmon, fresh boiled	Kokok	58.82	1.59	0.021	0.331	36.9	1.5	1.2
Salmon, fresh, average†				0.031	0.270	29.0	2.0	0.9
Salmon, canned†	Orphanage	68.36	1.79	0.007	0.214	20.9	7.7	1.3
Salmon, salt	Orphanage	55.10	16.02	0.040	0.185	19.5	8.4	1.0
Salmon, salt	Orphanage	55.38	16.55	0.020	0.182	23.5	4.3	0.3
Salmon, salt, average†				0.030	0.184	21.5	6.4	0.7
Salmon eggs, smoked†	Kokok	30.75	2.18	0.968	0.603	41.2	19.3	6.5
Tipmuk	Kokok	54.78	3.15	0.827	0.549	18.0	24.2	0
Tipmuk	Eek	61.57	2.57	0.545	0.442	12.8	23.8	0
Tipmuk, average†				0.686	0.496	15.4	24.0	0
Seal, red meat, dried	Kokok	37.70	2.93	0.013	0.475	53.5	5.9	0.5
Seal, red meat, dried	Kokok	64.28	1.34	0.019	0.175	32.8	1.1	0.5
Beluga, red meat, dried	Kokok	23.83	3.34	0.016	0.610	67.5	0.5	3.3
Seal, beluga, average†				0.016	0.419	51.3	2.5	1.4
Reindeer, dried	Bethel	11.09	3.54	0.028	0.446	68.8	14.9	1.7
Reindeer, canned†	Orphanage	62.82	2.37	0.004	0.202	24.9	7.9	2.0
Seal oil	Kokok	0.18	0.02	0	0	0	99.8	0
Seal oil with blubber	Eek	32.91	0.64	0.007	0.092	16.3	57.0	0
Seal oil, average†				0.004	0.046	8.2	78.4	0
Reindeer, tallow†	Orphanage	0	0.02	0	0	0	100.0	0
Cottonseed oil (scoco)†	Orphanage	0	0.01	0	0	0	100.0	0
Onions, evaporated†	Orphanage	14.31	5.10	0.183	0.378	14.2	1.0	65.3
Bayo beans, dried†	Orphanage	10.88	3.75	0.172	0.346	23.5	0.8	61.1
Wild rhubarb greens†	Kokok	91.45	0.89	0.037	0.024	2.1	....	5.5
Salmonberries	Kokok	85.36	0.55	0.014	0.045	2.1	0.9	11.0
Salmonberries	Eek	84.48	0.45	0.014	0.041	1.9	1.1	12.1
Blueberries	Eek	87.31	6.20	0.012	0.013	0.6	0.7	11.2
Thimbleberries	Bethel	86.79	0.52	0.022	0.033	1.1	0.4	11.2
Berries, average†				0.016	0.033	1.4	0.8	11.4
Jam, rhubarb	Orphanage	59.87	0.43	0.016	0.019	0.6	0.1	39.0
Jam, salmonberry	Orphanage	39.85	0.26	0.009	0.030	0.4	0.6	58.9
Jam, blueberry	Orphanage	55.35	0.17	0.011	0.031	0.4	1.1	42.9
Jam, average†				0.012	0.027	0.5	0.6	46.9
Bread†	Orphanage	36.54	0.74	0.018	0.131	7.9	0.7	54.1
Pilot bread†	Orphanage	13.68	1.89	0.016	0.097	8.5	2.0	74.0
Pancake	Kokok	54.66	0.21	0.009	0.044	4.9	4.0	36.2
Pancake	Eek	40.04	0.45	0.011	0.052	7.0	7.9	44.6
Pancake	Eek	44.89	0.45	0.007	0.045	6.5	5.7	42.5
Pancake, average†				0.009	0.047	6.1	5.9	41.1
Agutak	Kokok	9.34	2.26	0.030	0.047	3.0	67.9	17.5
Agutak	Kokok	75.20	0.46	0.013	0.067	3.6	13.0	7.7
Agutak	Kokok	16.52	0.68	0.023	0.175	11.1	66.6	5.1
Agutak	Eek	80.21	0.64	0.019	0.084	4.4	2.3	12.5
Agutak, average†				0.021	0.093	5.5	37.5	10.7
Eggs, dried	Orphanage	7.37	3.54	0.203	0.800	38.2	37.3	13.6
Ptarmigan, dried	Eek	21.53	4.26	0.033	0.739	70.6	1.2	0
Salmon back, dried	Kokok	43.95	7.65	1.956	0.532	42.7	5.9	0
Birch shelf fungus ash	Bethel	3.95	77.01	12.720	1.098	....	....	....
			Gm./100 cc.	Gm./liter	Gm./liter			
Kuskokwim River water	Bethel	.....	0.024	0.015	0.001	....	....	....

* Values are given in percentage of food as obtained.
† Values used in estimating composition of diets.

undoubtedly enter the Kepnuk diet occasionally, the average amounts used are probably insignificant.

The original analytic data on the composition of specimens of food obtained in the field are given in table 2, in which the individual and

average values employed in the detailed estimation of the composition of the diets are marked with daggers. Data for other foods were taken from the estimations of Sherman[7] or Bridges.[8] Values for needlefish were estimated as those for "sardines in oil;" those for other fish, as an average of the values for protein and fat in cod, herring, pickerel, tomcod and whitefish. With the average for protein thus derived, Sherman's values for calcium and phosphorus in average fish were used. Bridges' values for protein and fat in rabbits were used for "other animals," and Sherman's values for calcium and phosphorus in average meat were applied in a corresponding manner. For livers and organs a composite was used of values for beef heart, liver, sweetbreads, kidney, marrow and tongue, goose liver, mutton liver, calf kidney and veal kidney. The values for birds are an average of those for duck and goose and for eggs of those for duck and goose eggs. For native roots averages for carrots, celery roots, scallions, radishes, turnips and onions were used, and for native greens, averages for cabbage, turnip tops, spinach, carrot tops, rhubarb greens (original) and beet greens. Candy was estimated as two-thirds cane sugar, one-sixth milk chocolate and one-sixth sweet chocolate.

The resulting values for estimated consumption of calcium, phosphorus, protein, fat and carbohydrate are summarized for the three settlements in tables 3 to 5. Some of the salient features of these tables are represented graphically in the chart.

Since the purpose of this analysis is essentially comparative and since its object is to determine, if possible, what differences in the diets of the three settlements can be correlated with their respective incidences of dental caries, it is convenient to consider together the three tables and the graph. It will be recalled that Kepnuk had little caries, Eek much and the orphanage an intermediate amount.

The analysis of the orphanage diet (table 3), depending on more precise data than the others, may be taken as a basis for comparison. This diet, when one considers the age group involved, appears to be adequate in caloric value by ordinary standards and departs from those standards chiefly in being somewhat high in protein, low in calcium and high in phosphorus. On the other hand, the diet at Eek, by the same standard, is very high in both protein and fat and low in carbohydrate, while that at Kepnuk has similar characteristics accentuated to an extreme degree, the carbohydrate being reduced to an extraordinarily low level. The ingestion of glycogen in fresh tissue,

7. Sherman, H. C.: The Chemistry of Food and Nutrition, ed. 5, New York, The Macmillan Company, 1937.

8. Bridges, M. A.: Food and Beverage Analyses, Philadelphia, Lea & Febiger, 1935.

TABLE 3.—*Estimated Consumption of Calcium, Phosphorus, Protein, Fat and Carbohydrate at the Moravian Orphanage* *

Food	Estimated Consumption		Calcium		Phosphorus		Protein		Fat		Carbohydrate	
	Lb.	%	Lb.	%	Lb.	%	Lb.	%	Lb.	%	Lb.	%
Fish	191.6	18.6	0.052	9.6	0.509	30.0	50.8	38.6	8.9	17.3	1.5	0.5
Meat, eggs	150.2	14.6	0.010	1.8	0.317	18.7	35.2	26.8	17.2	33.4	2.4	0.8
Fat, oil	11.0	1.1	0.001	0.2	0.001	0.1	0.1	0.1	9.9	19.2	0	0
Milk	108.4	10.6	0.307	56.5	0.205	12.1	8.6	6.5	8.7	16.9	16.4	5.8
Raw vegetables	23.6	2.3	0.013	2.4	0.010	0.6	0.3	0.2	0	0	1.2	0.4
Cooked vegetables	36.4	3.5	0.043	7.9	0.016	1.0	0.7	0.5	0	0	3.5	1.2
Dried beans, peas	14.8	1.4	0.018	3.3	0.056	3.3	3.3	2.5	0.2	0.4	9.4	3.3
Berries, fresh fruit	96.5	9.4	0.013	2.4	0.029	1.7	1.1	0.8	0.6	1.2	11.6	4.1
Preserved fruit	17.2	1.7	0.009	1.7	0.012	0.7	0.3	0.2	0.1	0.2	10.1	3.6
Cereals	74.5	7.3	0.023	4.2	0.153	9.0	8.5	6.5	2.2	4.3	55.3	19.5
Flour products	274.7	26.8	0.048	8.8	0.356	21.0	21.7	16.5	2.2	4.3	148.1	52.3
Sugar, sirup, candy	25.4	2.5	0.003	0.9	0.007	0.4	0.2	0.2	0.6	1.2	23.2	8.2
Cocoa, gelatin	3.2	0.3	0.004	0.7	0.021	1.2	0.8	0.6	0.9	1.7	1.1	0.4
Total, lb. per yr.	1,027.5		0.544		1.692		131.6		51.5		283.8	
Total, Gm. per day	1,280		0.676		2.10		163.7		64.1		353	
Calories per day	2,644		.....		.....		655		577		1,412	
Calories, percentage	.....		.....		.....		24.7		21.8		53.4	
Percentage of diet dry	.....		0.114		0.354		27.5		10.8		59.3	

* Values are given as pounds per person per year.

TABLE 4.—*Estimated Consumption of Calcium, Phosphorus, Protein, Fat and Carbohydrate at Eek* *

Food	Estimated Consumption		Calcium		Phosphorus		Protein		Fat		Carbohydrate	
	Lb.	%	Lb.	%	Lb.	%	Lb.	%	Lb.	%	Lb.	%
Fish	500	46.6	0.257	77.6	1.989	67.7	179.5	64.0	56.1	45.1	6.6	5.8
Meat, eggs	280	26.1	0.036	10.9	0.805	27.4	88.4	31.5	25.4	20.4	3.7	3.3
Fat, oil	41	3.8	0.001	0.3	0.012	0.4	2.1	0.7	35.6	28.6	0	0
Roots, raw	2	0.2	0.001	0.3	0.001	0.03	0	0	0	0	0.2	0.2
Cooked roots, greens	8	0.7	0.007	2.1	0.002	0.1	0.1	0.04	0	0	0.5	0.4
Dried beans	0.5	0.05	0.001	0.3	0.002	0.1	0.1	0.04	0	0	0.3	0.3
Berries	80	7.5	0.010	3.0	0.026	0.9	1.1	0.4	0.6	0.5	9.1	8.0
Rice	5	0.5	0.001	0.3	0.005	0.2	0.4	0.1	0	0	4.0	3.5
Flour products	110	10.2	0.013	3.9	0.090	3.1	8.3	3.0	4.8	3.9	57.1	50.3
Sugar, candy	32	2.8	0.003	0.9	0.003	0.1	0.1	0.04	0.2	0.2	31.6	27.9
Agutak	4	0.4	0.001	0.3	0.004	0.1	0.2	0.1	1.5	1.2	0.5	0.4
Total, lb. per yr.	1,072.5		0.331		2.939		280.3		124.2		113.6	
Total, Gm. per day	1,335		0.412		3.66		349		154		141	
Calories per day	3,350		.....		.....		1,396		1,389		565	
Calories, percentage	.....		.....		.....		41.7		41.5		16.8	
Percentage of diet dry	.....		0.062		0.552		52.7		23.3		21.3	

* Values are given as pounds per person per year.

TABLE 5.—*Estimated Consumption of Calcium, Phosphorus, Protein, Fat and Carbohydrate at Kepnuk* *

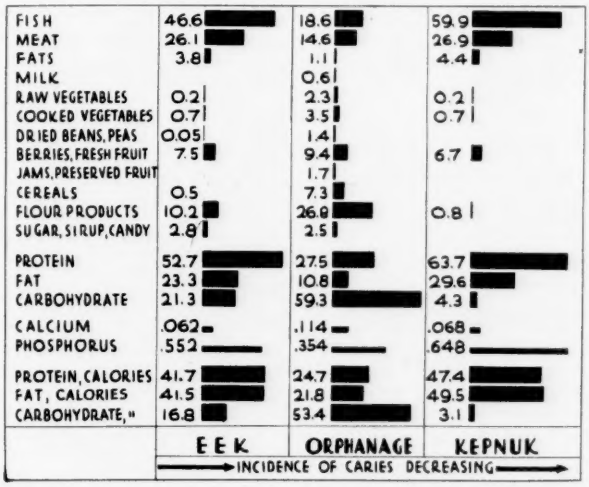
Food	Estimated Consumption		Calcium		Phosphorus		Protein		Fat		Carbohydrate	
	Lb.	%	Lb.	%	Lb.	%	Lb.	%	Lb.	%	Lb.	%
Fish	713	59.9	0.253	76.7	2.068	65.3	192.0	61.9	72.1	50.0	2.7	13.2
Meat, eggs	320	26.9	0.055	16.7	1.041	32.9	112.5	36.2	27.4	19.0	3.4	16.6
Fat, oil	53	4.4	0.002	0.6	0.023	0.7	4.1	1.3	42.2	29.2	0	0
Roots, raw	2	0.2	0.001	0.3	0.001	0.03	0	0	0	0	0.2	1.0
Roots, greens (cooked)	8	0.7	0.007	2.1	0.002	0.1	0.1	0.3	0	0	0.5	2.4
Berries	80	6.7	0.010	3.0	0.026	0.8	1.1	0.4	0.6	0.4	9.1	44.5
Pancakes (seal oil)	10	0.8	0.001	0.3	0.005	0.2	0.6	0.2	0.6	0.4	4.1	20.0
Agutak	4	0.3	0.001	0.3	0.004	0.1	0.2	0.1	1.5	1.0	0.5	2.4
Total, lb. per yr.	1,190		0.330		3.170		310.6		144.4		20.5	
Total, Gm. per day	1,480		0.411		3.94		386		179		25.5	
Calories per day	3,258		.....		.....		1,544		1,612		102	
Calories, percentage	.....		.....		.....		47.4		49.5		3.1	
Percentage of diet dry	.....		0.068		0.648		63.7		29.6		4.3	

* Values are given as pounds per person per year.

such as needlefish, would increase this level somewhat, but probably not to a marked degree.

The major characteristics of the orphanage diet are evidently determined by its two preponderant food groups: fish and meat, which constitute about one third of the food intake and contribute more than half the protein and fat, and flour products (largely bread) and cereals, which account for more than a third of the food eaten and contribute nearly three fourths of the total carbohydrate. Both of these food groups likewise contribute disproportionately little calcium, lack of which appears to be barely prevented by the presence of milk.

The characteristics of the diets at both Eek and Kepnuk are, of course, determined in large measure by the preponderance of fish, meat



Estimated percentage distribution of main food groups, dietary components and calories at the three settlements.

and fat. At Kepnuk these foods are estimated to comprise more than 90 per cent of the food eaten. At Eek, on the other hand, the inclusion of considerable quantities of white man's food (chiefly flour products and sugar) diminishes the relative importance of the animal foods and introduces considerable quantities of carbohydrate.

At both Eek and Kepnuk the totals for calcium, according to the tables, appear low enough to constitute a definite deficiency, aggravated in both instances by the disproportionately high totals for phosphorus. These values, however, are subject to correction in undetermined degree. The data include no measure of the calcium undoubtedly contributed at both settlements by the ingestion of bones, which, providing calcium in considerable excess over phosphorus, both raise the actual calcium levels and tend to overcome the apparently disproportionate calcium-

phosphorus ratios. Moreover, the natives at both settlements indulge widely in the practice of chewing the preparation of fungus ash alluded to previously. This material, as indicated in table 2, is rich in calcium and contains little phosphorus. Some of it is undoubtedly swallowed. It seems probable that these practices actually correct the apparent calcium deficiencies indicated in tables 4 and 5, perhaps in equal degree at the two settlements.

Other characteristics of these diets, as they relate particularly to dental caries, are not implicit in the tables, but may be assumed roughly from them. The potential reaction of the orphanage diet seems to be at least moderately acid, since, although base-forming foods are present, they are overshadowed quantitatively by the acid-forming fish, meat and grain foods. On the other hand, it appears that the potential reaction of the diets at Eek and Kepnuk is even more strongly acid. At Eek the foods yielding excess base (roots, greens, beans and berries) constitute less than 10 per cent of the total diet, and at Kepnuk the proportion is even lower. The inclusion of white man's foods which yield an excess of acid at Eek hardly seems to alter the character of the diet in this respect as compared with that of Kepnuk. On the other hand, the effect of additional base-forming elements not included in the tables, particularly calcium, as noted previously, again probably modifies the extreme picture otherwise implied.

Of the vitamins only D need be considered for the purposes of this report. Adequate quantitative data on this point are again lacking, and only a rough estimation is possible. The estimated values for cod liver oil suggest that from this source alone the diets at Eek and Kepnuk are richer in vitamin D than that at the orphanage, and the difference would be only partly made up from the irradiated evaporated milk at the orphanage, the vitamin D content of the latter being comparatively low. On the other hand, many fish oils are known to be rich in vitamin D. According to Bills,[9] the liver oils of two types of salmon are thirteen and four times as potent in vitamin D, respectively, as cod liver oil; oil from the entire body of the herring is equivalent to cod liver oil in vitamin D content, and oil from the trimmings of salmon has 40 per cent of the potency of cod liver oil. Data on other fish used by these Eskimos are not available. It seems reasonable to assume that such sources supply the natives with an abundance of the vitamin. In view of the definitely higher intake of fish at Kepnuk and Eek than that at the orphanage, which augments the estimated intake of cod liver oil and milk as previously noted, the amounts of vitamin D available at Kepnuk and Eek are probably at least as high as, and perhaps higher

9. Bills, C. E.: Physiol. Rev. **15**:1, 1935.

than, that at the orphanage. The available data hardly permit comparison of Kepnuk and Eek in this respect.

Table 6 presents an additional group of data, which are not directly related to the analysis with which this report is primarily concerned but are of interest in themselves. The data were obtained from records of native purchases which were supplied by Mr. Willard R. Olsen, a trader in Bethel. They relate to natives chiefly from Bethel and Quithluk and comprise sixty-two orders placed during two periods: from February to April 1936 and in June 1936. Only foods are given in

TABLE 6.—*Summary of Data from Records of Smeaton's Store at Bethel, Alaska* *

Food	Total Sales		Percentage of Total Expenditure	Percentage of Expenditure for Food	Price per Pound	Pounds Purchased	Percentage of Total Food by Weight
	Number	Amount					
Flour	43	$300.00	18.5	45.3	$0.06	5,000.0	71.3
White sugar	36	103.00	6.4	15.6	0.10†	1,052.0	15.6
Rock salt‡	4	10.00	0.6	1.5	0.05	200.0	2.8
Canned milk	13	26.50	1.6	4.0	0.167	150.0	2.1
Rice	8	15.00	0.9	2.3	0.10	150.0	2.1
Tea	43	93.50	5.8	14.2	1.00	93.5	1.3
Coffee	18	35.00	2.2	5.3	0.50	70.0	1.0
Lard	16	15.50	1.0	2.3	0.25	62.0	0.9
Table salt	17	6.00	0.4	0.9	0.125‖	48.0	0.7
Pilot bread	11	11.20	0.7	1.7	0.25	45.0	0.6
Butter	8	18.00	1.1	2.7	0.50	36.0	0.5
Baking soda	10	4.30	0.3	0.7	0.125‖	33.0	0.5
Corn meal	2	3.00	0.2	0.5	0.15‖	20.0	0.3
Candy§	15	5.20	0.3	0.8	0.40‖	16.0	0.2
Onions	2	2.00	0.1	0.3	0.20‖	10.0	0.1
Zwieback	8	4.00	0.2	0.6	0.50‖	8.0	0.1
Baking powder	7	1.75	0.1	0.3	0.25‖	7.0	0.1
Oatmeal	1	0.75	...	0.1	0.15‖	5.0	0.1
Potatoes	1	0.50	...	0.1	0.10‖	5.0	0.1
Peanut butter	3	2.00	0.1	0.3	0.80‖	2.5	...
Jam	2	2.00	0.1	0.3	0.80‖	2.5	...
Oranges	2	0.75	...	0.1	0.25‖	3.0	...
Raisins	2	0.75	...	0.1	0.33‖	2.3	...
Pepper	1	0.25	...	...	....	...	...

* Compiled from sixty-two native orders placed during February, March, April and June 1936 in exchange for animal pelts.

† In sacks, $0.09; in boxes, $0.125.

‡ Used in salting fish.

§ An undetermined amount of additional candy is sold to children over the counter without record.

‖ Approximate.

the table, but all the foods recorded on the orders are included, being arranged in order of preponderance by weight.

COMMENT

If the incidence of dental caries at the three settlements studied is related in a causative manner to any one or any combination of the dietary conditions included in the foregoing analysis, some degree of quantitative correspondence may be expected to exist between these conditions. If they are directly causative, the degree to which they occur should be more marked at the orphanage than at Kepnuk and more marked at Eek than at either of the other settlements. If the conditions

are protective or preventive, a reverse relationship ought to hold true; if both types of conditions are present, a suitable balance between them should be present to account for the difference in incidence of the disease.

It is evident that for many of the conditions widely held responsible for dental caries or for its relative absence,[2] the data indicate no such correlation. There is no simple relation between the amounts of any of the major components of the three diets and the corresponding levels of dental caries at the three settlements. If one were to exclude the orphanage and compare only Kepnuk and Eek in the manner employed in several previous investigations in this field, several striking correlations might appear. The Eek diet is higher in carbohydrate than that of Kepnuk, and most of the carbohydrate is contributed by cereal or grain foods and sugar. Evidence obtained from animal experiments [10] may suggest that the lower levels of both fat and protein at Eek as compared with those at Kepnuk may be charged with significance in the same direction; yet at best these differences are small, the actual levels of both fat and protein being high at both settlements. Likewise, it is possible that the diet at Eek includes smaller amounts of both vitamin D and calcium than that of Kepnuk. The content of vitamin D in the Eek diet may be reduced because of encroachment on the intake of fish by the use of white man's food. The intake of calcium at Eek may suffer similarly because of a possible diminution in amount of ingested bones, or perhaps by partial displacement of the native habit of chewing fungus ash, as part of the white man's influence.

Comparison with the orphanage diet, on the other hand, makes it evident that these apparent correlations are largely, if not entirely, invalid. The orphanage, with an intermediate incidence of caries, has the highest intake of carbohydrate, including the highest level of cereal and grain foods (but not of sugar, as will be noted). It shows the lowest levels of protein and fat. Its content of vitamin D would seem to be lower than that of either of the other settlements, while its calcium level, in the absence of ash chewing and doubtless with less ingestion of bone, is probably not higher. On the whole the orphanage diet, in view of its content of carbohydrate, made up largely of cereal and grain products, its calcium and its vitamin D level and its evident potential acidity, seems according to several conceptions to be one that ought to induce a high incidence of dental caries. That it has not done so and that, in general, the correlations to be expected from several prevailing views of dental caries do not hold are evidence against the validity of these

10. Rosebury, T., and Karshan, M.: Susceptibility to Dental Caries in the Rat: Influence of Calcium, Phosphorus, Vitamin D and Corn Oil, Arch. Path. **20**:697 (Nov.) 1935.

views or suggest that they fail to take cognizance of some other factor more directly responsible for the disease or for its absence. It seems hardly likely that the dental care received by the orphanage children or their practice of brushing the teeth alters this picture in any appreciable way.

The chart shows the quantitative correlation of single food groups, such as sugar, with the incidence of dental caries at the three settlements. Table 1 defines this relationship further and lists three other individual foods which show quantitative correlation with caries—reindeer tallow and commercial fats, both undoubtedly coincidental, and pilot bread.

The data indicate that the amount of white sugar used at Eek is greater than the combined total of white and brown sugar and sirup used at the orphanage. These foods are used in insignificant amounts at Kepnuk. This may be a factor of importance in the relative prevalence of dental caries at the three settlements. It must be remembered, however, that the sugar used at Eek is taken chiefly in solution in tea. It is difficult to assign to sugar in this form, as a food acting independently of other carbohydrate, a primary role in the causation of dental caries.

The remaining correlated factor, pilot bread, is interesting in view of its apparent correspondence with data previously obtained by us [11] on the etiologic significance of particles of coarse raw cereal in experimental dental caries in rats. We have since determined, as a sequel to the present study, that pilot bread is capable of replacing coarse raw rice or corn in experimental diets and thus of producing fissure caries and proximal contact caries in rats. These and our earlier experimental data, in conjunction with the data in the present report, form the basis of a hypothesis of dental caries in which pilot bread is postulated as a type of food primarily responsible for dental caries in young persons. This concept, with the experimental data bearing on it, has been alluded to briefly elsewhere [12] and will be presented in detail in a later report.

SUMMARY

The diets and the dietary habits of Eskimos at three Alaskan settlements are described, and data are presented on their composition. Of the three settlements, one (Kepnuk) is primitive and isolated and has little dental caries; another (Eek) is primitive, but has a resident white trader, and has much dental caries, while a third (a Moravian

11. Rosebury, T.; Karshan, M., and Foley, G.: J. Dent. Research **13**:379, 1933; J. Am. Dent. A. **21**:1599, 1934.

12. Rosebury, T.: J. Dent. Research **16**:308, 1937.

orphanage), despite more extensive influence of the white man's diet than is present at either of the others, has an intermediate incidence of dental caries.

Most of the dietary conditions commonly held to be responsible for dental caries or its absence cannot be correlated with the incidence of dental caries at the three settlements. These uncorrelated conditions include dietary carbohydrate in general, cereal and grain foods, dietary protein and fat, calcium and phosphorus and probably vitamin D and the potential reaction of the diets. These conditions consequently either lack influence on, or play secondary roles in, the causation of dental caries among these people.

Consumption of sugar, correlated with the occurrence of dental caries at the three settlements, may be of importance in the development of the disease, but since at Eek, where the largest amount of sugar is used, most of it is ingested in dissolved form (in tea), its importance as a primary cause of dental caries appears doubtful.

The only other food to which significance may be attached, the use of which is correlated with the prevalence of dental caries at the three settlements, is pilot bread or ship biscuit. Allusion is made to a hypothesis which implicates foods of this kind in the causation of dental caries; this view is based on the data in this report and on other experimental findings.

HOSPITAL INFECTIONS

II. NASOPHARYNGEAL FLORA AND DISEASE OF THE RESPIRATORY TRACT IN INFANTS

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A survey of the records of the Infants' Hospital of Boston for the years 1935 and 1936 showed that 185 of the 1,455 patients admitted during the two year period contracted infections in the hospital.[1] Acute infections of the respiratory tract made up 59.8 per cent of the secondary disorders; the next largest group were cutaneous infections, which made up 15.6 per cent. It was apparent that the 906 patients with acute infections of the respiratory tract, including pneumonia, admitted during the two year period as well as persons with similar infections and carriers among the staff, attendants and visitors presented the great source of danger for the other infants in the wards.

A concurrent study of hospital infections in the same institution confirmed the findings derived from the survey of the records.[2] In the cases in which bacteriologic examinations were made direct personnel to patient infections were found to predominate. Because of the importance of the infections of the respiratory tract present in the patients on admission, an analysis of such infections, together with an investigation of the flora in the patients' respiratory tracts at the time of admission, was thought desirable.

CLASSIFICATION OF PATIENTS

Total admissions to the wards during the ten month period of the present study (June 1937 through March 1938) numbered 635.

From the Department of Pediatrics, Harvard Medical School, the Department of Communicable Diseases, Harvard School of Public Health, and the Infants' and Children's Hospitals, Boston.

1. McKhann, C. F.; Steeger, A., and Long, A. P.: Hospital Infections: Survey of the Problem, Am. J. Dis. Child. **55**:579 (March) 1938.

2. Long, A. P.; McKhann, C. F., and Cheney, L. L.: Am. J. Pub. Health, to be published.

Acute diseases of the respiratory tract accounted for 261 of the 323 patients admitted for infectious disorders. Patients with infections of the upper part of the respiratory tract, including otitis media and cervical adenitis, numbered 145, and those with pneumonia or bronchitis numbered 116.

Other infectious diseases were meningitis due to meningococci, influenza bacilli, pneumococci, tubercle bacilli and Bacillus proteus; sepsis due to hemolytic streptococci, staphylococci, pneumococci, influenza bacilli and colon bacilli; dysentery (2 cases) due to the Sonne type of dysentery bacilli; pustular dermatitis; erysipelas; tuberculosis; thrush; Vincent's infection, and pertussis. There was 1 patient who was known to have been exposed to chickenpox and who subsequently had the disease in the isolation ward.

The greatest seasonal variation was shown among diseases of the respiratory tract. The bronchitis-pneumonia group accounted for almost

TABLE 1.—*Admissions for Infectious Diseases (by Month)*

Diagnosis	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Total
Infections of the upper part of the respiratory tract, including cervical adenitis, otitis	14	9	29	10	13	16	12	20	10	12	145
Bronchitis and pneumonia	12	7	6	4	14	8	13	14	14	24	116
Meningitis, all forms	1	1	1	3	2	2	3	2	2	1	18
Sepsis, all forms	..	..	..	1	2	5	..	1	1	..	10
Other infections	8	..	2	5	5	2	..	2	3	7	34
Total	35	17	38	23	36	33	28	39	30	44	323

twice as many admissions in March as in any other one month and for six times as many admissions in that month as in September, in which there were only 4 admissions in this category. In contrast, there was a large number of admissions for infections of the upper part of the respiratory tract in August; the largest number of admissions for this type of infection occurred in that month. The high figure in August brought the total number of admissions for infections of the respiratory tract to essentially the same level as that seen in March (table 1).

BACTERIOLOGIC STUDIES

Throughout the last six months of the ten month period bacteriologic studies of nasopharyngeal cultures were made on all patients admitted to the hospital. To determine the organisms present in the individual patient on admission, material for culture was taken from the nasopharynx of each patient within the first twenty-four hours of hospitalization.

It was appreciated that the organisms found in the noses and throats of patients suffering from infections of the respiratory tract

might not in themselves be the causative agents of the infections. This was especially applicable to infections of the upper part of the respiratory tract, the etiologic agents of which are accepted to be ultramicroscopic filter-passing viruses.[3] However, it was felt that the presence of the virus might result in the activation of organisms already in the respiratory passages and also by its action help to make these passages a more suitable habitat for secondary invaders.[4] Since the cultivation of the virus of infections of the upper part of the respiratory tract is not on a basis applicable to a problem of this kind, information in relation to those bacterial organisms that might be either the cause or secondary invaders were sought. The pneumococcus lent itself best to the study, because of the subdivision into the thirty types for which type-specific diagnostic serums were available.[5] In regard to Streptococcus haemolyticus, presumptive evidence was gathered through the determination of the dissociation variants of each strain isolated. The dissociation phases of the strains of influenza bacilli isolated were also determined.

Conclusions could not be drawn in regard to the significance of such organisms as staphylococci and indifferent, or gamma, streptococci, which were present in patients in the wards at all times and also were common among the members of the attending staff.

Material was collected on separate swabs from each nostril and from the throat. In taking the material for culture from the throat, an effort was made with a tongue depressor to induce gagging in order to collect material from the bronchial tree. The three swabs were immediately inserted into a tube containing 3 cc. of hormone broth with 1 per cent horse blood.

The blood broth tubes containing the swabs were incubated at 37 C. (98.6 F.) for two hours. Hormone agar plates containing 5 per cent horse blood were streaked from the broth. After incubation for twenty-four hours the different types of colonies were picked, smeared and stained with Gram's stain for partial identification. Representative colonies showing alpha hemolysis were picked to a second blood agar plate for the purpose of obtaining pure cultures. This was likewise done with colonies showing beta hemolysis to differentiate between streptococci and Haemophilus haemolyticus (Bacillus X). Colonies

3. (*a*) Dochez, A. R.: Medicine **12**:245, 1933. (*b*) Long, P. H.; Doull, J. A.; Bourne, J. M., and McComb, E. J.: J. Exper. Med. **53**:447, 1931. (*c*) Dochez, A. R.; Mills, K. C., and Kneeland, Y., Jr.: ibid. **63**:559, 1936.

4. Dochez, A. R.; Mills, K. C., and Kneeland, Y., Jr.: Disease of the Upper Respiratory Tract: Problems Connected with Etiology and Prophylaxis, J. A. M. A. **101**:1441 (Nov. 4) 1933.

5. Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: J. Exper. Med. **55**:531, 1932.

in which the type of hemolysis was questionable were picked to peptone blood agar plates, as recommended by Mueller,[6] for further differentiation. Colonies of organisms resembling Haemophilus influenzae were picked to chocolate agar.

Classification of Organisms.—No classification was made of organisms commonly inhabiting the nasopharynx, such as the gram-negative diplococci, diphtheroids and miscellaneous gram-positive bacilli and cocci, these being noted merely as "gram-negative cocci, unclassified" or "gram-positive bacilli, unclassified." Staphylococci were noted as either albus or aureus, hemolytic or nonhemolytic. Gram-negative bacilli other than H. influenzae and Bacillus X were inoculated on eosin–methylene blue agar plates, and if lactose fermenters were found they were noted as belonging to the colon-aerogenes group.

Pneumococci, streptococci and H. influenzae were further studied and classified as follows:

Pneumococci: Pure cultures of alpha hemolytic gram-positive cocci were inoculated into dextrose infusion broth containing 0.5 per cent rabbit serum as suggested by Shaffer and Enders[7] and were allowed to incubate at 37 C. for four to six hours, the time for the production of a suspension of proper density varying somewhat with individual strains. A bile solubility test was then done, bile-insoluble organisms being considered as streptococci (viridans) and bile-soluble organisms as pneumococci. The pneumococci were then typed by the Neufeld reaction as described by Sabin.[8] Type-specific rabbit serums prepared by the Lederle Laboratories were used for this purpose. In case of failure to type, a white mouse was given an intraperitoneal injection of 0.5 cc. of the broth suspension of pneumococci. If the mouse did not die within five days it was killed, and if no organisms could be recovered from the peritoneal cavity or the cardiac blood the organism in question was considered to be an avirulent, rough (*R*) strain, which finding checked in the majority of cases with the colonial characteristics on blood agar.

Streptococci: Gram-positive cocci occurring in streptococcic forms but exhibiting no hemolysis on blood agar were classified as nonhemolytic or gamma streptococci. Streptococcus viridans was isolated and classified in the manner described. Pure cultures of beta hemolytic streptococci were further studied in relation to their dissociation phase or variant after the method of Ward and Lyons.[9] This method consisted

6. Mueller, J. H., and Whitman, L.: J. Bact. **21**:219, 1931.

7. Shaffer, M. F., and Enders, J. F.: J. Exper. Med. **64**:281, 1936.

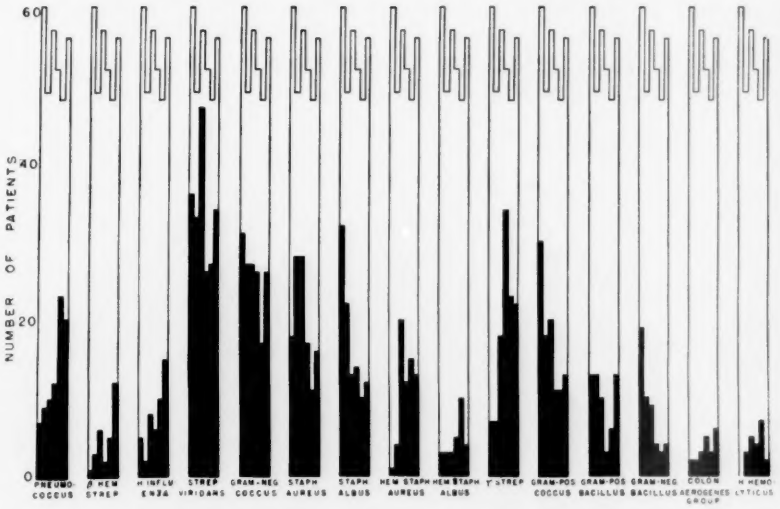
8. Sabin, A. B.: Immediate Pneumococcus Typing Directly from Sputum by the Neufeld Reaction, J. A. M. A. **100**:1584 (May 20) 1933.

9. Ward, H. K., and Lyons, C. J.: J. Exper. Med. **61**:515, 1935.

in the inoculation of the organisms into neopeptone broth, which after incubation for eighteen hours was plated out on neopeptone glycerin agar containing 15 per cent horse blood. After sixteen or eighteen hours' incubation the colonial characteristics were studied with a colony microscope and the variant noted as F, M or C.

H. Influenzae: Gram-negative bacilli resembling H. influenzae were isolated in pure culture on chocolate agar. Studies were made as to the characteristics of colonial morphologic characters and serologic reactions in relation to their dissociation phase.

The bacteriologic findings in relation to the total number of cultures made during each month are shown in the accompanying illustration.



Monthly distribution (October through March) of organisms isolated in cultures made on admission of patients to the hospital.

Each grouped classification of species is plotted separately by months against the total cultures made in each month. In this manner is shown the relative change from month to month of the incidence of each group. The figures for the pneumococci include only those which were type specific and for which the types were determined.

The basic nasopharygeal flora was made up of organisms commonly regarded as nonpathogens, such as Str. viridans, gram-negative cocci, staphylococci, indifferent, or gamma, cocci, unclassified gram-positive cocci and unclassified gram-positive and gram-negative bacilli, together with members of the colon-aerogenes group and the diphtheroids, and did not differ significantly from the flora found in the general

population.[10] There was close agreement between these observations and those of Kneeland,[11] who found by repeated cultures of material from infants during several months after birth that by the age of 8 months the nasopharyngeal flora of an infant becomes comparable to that of an adult.

Seasonal Variation in Flora.—Throughout the late fall and winter months there was an increase in the relative incidence of certain of the organisms usually considered nonpathogenic. The increase was most marked in the hemolytic forms of Staph. aureus and Staph. albus, the nonhemolytic forms of Staph. albus and the large unclassified gram-positive cocci showing some decrease in incidence. There was also a definite increase in the incidence of the indifferent, or gamma, streptococci. These nonpathogenic forms, considered by some to become on occasion secondary invaders in infections of the respiratory tract [10d] (along with the more pathogenic species), showed increases relatively parallel to or exceeding those of the pneumococci, hemolytic streptococci and H. influenzae. The latter groups of organisms showed definite increases in incidence throughout the late fall and winter months, the pneumococci reaching their peak in February and the hemolytic streptococci and influenza bacilli showing the greatest relative incidence in March. The incidence of the latter, or pathogenic, groups during these months was to be expected in view of the increased number of admissions for disease of the respiratory tract, chiefly of the bronchopulmonary group, during the same period. The parallel increase in incidence of certain of the nonpathogenic and pathogenic organisms in the patients on admission would appear to indicate a definite seasonal build-up and increase in transference from person to person of organisms other than those commonly associated with the flora of the respiratory tract. While no attempt was made to determine quantitatively the relative number of each type of organism in a given person, it was noted that during the winter months even the nonpathogenic forms appeared to be present in relatively greater numbers than in the earlier months.

Distribution of Specific Types of Pneumococci.—A classification of the strains of pneumococci isolated is given in table 2, to show the various types isolated in relation to illness in the patient. Twenty-two of the thirty types were isolated.[12] Types XIV and VI were found

10. (*a*) Williams, A.: J. Immunol. **6**:115, 1921. (*b*) Jordan, E. O.: J. Infect. Dis. **33**:416, 1937. (*c*) Bloomfeld, H.: Bull. Johns Hopkins Hosp. **32**: 33, 1936. (*d*) Shibley, G. S.; Hanger, F. M., and Dochez, A. R.: J. Exper. Med. **43**:415, 1926.

11. Kneeland, Y., Jr.: J. Exper. Med. **51**:617, 1930.

12. Types XXVI and XXX were considered identical with types VI and XV respectively and hence are not included.

to be the most common, accounting for almost one-half of the total number of strains isolated and for over one-half of all the attacks of pneumococcic pneumonia. It will be noted that only six of the twenty-three type XIV strains isolated were present in patients with conditions other than pneumonia and that none was present in a patient with no infection of the respiratory tract. Six of the sixteen type VI strains were present in conditions other than pneumonia; two were in patients with no infection of the respiratory tract. The next most frequent types isolated were found to be types XIX, XXIX, VII and XVIII. Types other than VI and XIV shown to be present in patients with pneumonia were type VII in 4 of the total of 49 cases of

TABLE 2.—*Pneumococci by Type and Diagnosis*

Type	Bronchitis and Pneumonia	Infection of the Upper Part of the Respiratory Tract	No Infection of the Respiratory Tract	Total
XIV	19	4	0	23
VI	11	3	2	16
XIX	3	..	1	4
XXIX	2	..	2	4
VII	4	..	..	4
XVIII	2	1	1	4
XX	1	2	..	3
I	2	..	1	3
XI	2	1	..	3
VIII	2	..	..	2
X	..	..	2	2
III	..	1	1	2
XXIII	..	1	1	2
XXI	..	..	1	1
XXII	..	..	1	1
XII	1	..	..	1
II	1	..	..	1
IX	1	..	..	1
XXIV	..	..	1	1
XVII	1	..	..	1
V	1	..	..	1
XV	..	..	1	1
Total	53	13	15	81

pneumococcic pneumonia studied, types XXIX in 2, type XIX in 2, type XVIII in 2, type XI in 2, type VIII in 2, type I in 2 and types XX, XII, II, IX, XVII, and V in 1 each. Thirty-two of the eighty-one strains isolated were present in patients with conditions other than pneumonia.

The findings become more significant when it is noted that the types of pneumococci isolated from patients with pneumonia in this age group [13] are not the same as those commonly obtained from adults

13. (*a*) Bullowa, J. G. M.: The Management of the Pneumonias, for Physicians and Medical Students, New York, Oxford University Press, 1937. (*b*) Smillie, W. G.: Tr. A. Am. Physicians **51**:407, 1936; Epidemiology of Lobar Pneumonia: Study of the Prevalence of Specific Strains of Pneumococci in the Nasopharynx of Immediate Family Contacts, J. A. M. A. **101**:1281 (Oct. 21) 1933. (*c*) Webster, L. T., and Hughes, J. P.: J. Exper. Med. **53**:535, 1931.

with the disease. It has been shown that the most common types in pneumonia in adults are types I, II, III, IV, V, VII and VIII and that among the most common types isolated from normal adults are types VI, XIV, XIX, XI and XVIII, types which in turn are commonly found in pneumonia of infants and children, as has been noted by Vinograd, Nemir and Park,[14] Bullowa and Greenbaum,[15] Andrews [16] and Nemir.[17]

From December 1936 to May 1938, which includes most of the total period of our study of hospital infections, of 122 patients with pneumonia admitted to the Infants' Hospital, 50 had involvement due to the type XIV pneumococcus, 10 to type VI and 8 to type XIX.

Thus it would appear that infants are susceptible to infection by types of pneumococci that adults carry with impunity. Because of the low carrier rate among infants it may be assumed that in infants pneumonia due to these organisms is in large part transferred from the attendant to the infant and is not due to invasion by an organism previously harbored by the patient.

Unclassifiable Pneumococci.—In addition to the type-specific pneumococci isolated, there have been at various intervals throughout the six month period organisms classified as rough, avirulent stains of pneumococci. These unclassified pneumococci are not included in the table or in the totals.

Hemolytic Streptococci.—The incidence of the hemolytic streptococcus among patients on admission was relatively low, only 29 of the 322 cultures having yielded it. Whether this indicates a low infantile carrier rate for the organism or is due to year to year and season to season variation of the incidence of streptococcic infections among the general population cannot be definitely stated. Nineteen of the twenty-nine strains isolated were shown to be present in patients with some form of infection of the respiratory tract. The relation of dissociation variant to diagnosis is shown in table 3. The most commonly observed variant based on colonial characteristics was the C variant. Although regarded as the least pathogenic, C forms were found in the majority

14. Vinograd, J.; Nemir, R. L., and Park, W. H.: Rapid Typing of Pneumococci by the Neufeld Reaction Directly from Laryngeal Swabs from Infants and Children, Am. J. Dis. Child. **51**:792 (April) 1936.

15. Bullowa, J. G. M., and Greenbaum, E.: Pneumococcic Pneumonia in Infants and Children, Am. J. Dis. Child. **53**:22 (Jan., pt. 1) 1937.

16. Andrews, E. T.: Lobar Pneumonia in Children: Differentiation of Recovered Pneumococci into Etiologic Groups and Their Familial Distribution, Am. J. Dis. Child. **54**:1285 (Dec.) 1937.

17. Nemir, R. L.: J. Pediat. **13**:219, 1938.

of instances in patients with infections of the respiratory tract and appeared to be the causative agent in many instances. M variants were the next most commonly observed forms and F forms the least frequently seen.

H. Influenzae.—All forty-seven strains isolated were of rough, respiratory type [18] except three, found to be of the smooth, virulent type. One of the latter forms occurred in conjunction with type XIV pneumococci in a case of pneumonia, one was isolated in conjunction with a hemolytic streptococcus (variant F) from the throat of a patient

TABLE 3.—*Hemolytic Streptococci by Diagnosis and Variant*

Diagnosis	Variant			Total
	F	M	C	
Infection of the upper part of the respiratory tract	..	..	3	3
Pneumonia with pneumococci	..	1	3	4
Pneumonia	2	..	..	2
Bronchial pneumonia	..	..	6	6
Bronchitis	..	..	2	2
Erysipelas	..	1	..	1
Impetigo	..	1	..	1
Other	1	5	4	10
Total	3	8	18	29

TABLE 4.—*Influenzae by Diagnosis and Associated Organisms*

Diagnosis	With Pneumococci	With Beta Streptococci	No Other Pathogens	Total
Lobar pneumonia	10*	3	4	17
Bronchial pneumonia	..	1	2	3
Bronchitis	1*	1	2	4
Infection of the upper part of the respiratory tract	4	..	7	11
Meningitis	..	1*	..	1
Other infections	4	..	7	11
Total	19	6	22	47

* One smooth strain in each group indicated.

with meningitis due to influenza bacilli and appeared to be serologically identical with the influenza bacillus isolated from the spinal fluid of the same patient, and one was isolated in conjunction with a pneumococcus type I and a hemolytic streptococcus (variant C) from the nasopharynx of a patient with acute bronchitis. Of the 4 patients with meningitis due to influenza bacilli admitted to the hospital during the period of bacteriologic study, there was only 1 from whose nasopharynx an influenza bacillus could be isolated. It is of some interest to note that of the forty-seven strains of H. influenzae isolated, twenty-five were found to be in conjunction with pneumococci or hemolytic streptococci,

18. Fothergill, L. D., and Chandler, C.: J. Immunol. **31**:401, 1936.

these associations occurring in 19 and 6 instances respectively. All of the smooth, virulent strains isolated were found in conjunction with other pathogens.

In table 4 are seen the distribution and incidence of H. influenzae with regard to the diagnosis of the condition and the pathogenic organism with which this organism was associated.

SUMMARY

The peak incidence of serious disease of the respiratory tract in infants, judged from admissions to the hospital, occurs in March. A second peak, of disease of the upper part of the respiratory tract not of a serious character, occurred in August.

Investigations of the nasopharyngeal flora of infants on admission to the hospital demonstrated a marked increase in the incidence of both pathogenic and nonpathogenic organisms throughout the winter months.

Ten per cent of the infants not suffering from bronchitis or pneumonia harbored a pneumococcus. The hemolytic streptococcus was present in 3 per cent of the patients not ill with disease of the respiratory tract.

Pneumonia in infants was commonly caused by organisms relatively nonpathogenic for adults. Certain types of pneumococci, notably XIV and VI, seemed particularly pathogenic for infants and were seldom present in infants free from disease of the respiratory tract. Because of the low carrier rate of the pathogenic organisms among infants, serious disease of the respiratory tract in these patients may be presumed to be due to infections derived from adult carriers rather than to follow the invasion of an organism previously harbored by the patient. Partial prevention of infection in infants might be achieved by diminishing the number of adult contacts and by the institution of better methods of interrupting direct transmission of nasopharyngeal organisms from the mother or nurse to the infant.

PROGNOSIS OF GLOMERULAR NEPHRITIS IN CHILDHOOD

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A study of the outcome of glomerular nephritis in childhood, similar to that reported from the Stanford University Medical School,[1] was undertaken at the University of Rochester Medical School, Rochester, N. Y. The earlier survey was based on 186 children seen in the children's service of the Stanford University Medical School from 1920 to 1936 and demonstrated a much higher percentage of cases of chronic and fatal glomerular nephritis than had previously been found by other observers. A similar study, done subsequently in Milwaukee,[2] demonstrated for the younger age groups a prognosis as serious as that found in the Stanford series.

Several reasons have been advanced for these discrepancies in statistics, the chief one being lack of agreement in classification of the condition, failure of recognition of the latent stage of glomerular nephritis, failure to make quantitative urinalyses of concentrated urine and selection in sampling of the Stanford group because of Dr. Addis' reputation. Another possibility to be considered was that glomerular nephritis might differ geographically.

With the last possibility in mind, a study was made of cases of glomerular nephritis observed in the children's service of the University of Rochester Medical School. The same classification and similar methods of examining the urine were employed in the present study as were used in the previous study at Stanford.

The series [3] consists of 146 children from 1 to 15 years of age in whose cases the diagnosis of glomerular nephritis was made between

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From the Department of Pediatrics, the University of Rochester School of Medicine and Dentistry.

1. Snoke, A. W.: Stages, Prognosis and Duration of Glomerular Nephritis in Childhood, Am. J. Dis. Child. **53**:673 (March) 1937.

2. Murphy, F. D., and Rastetter, J. W.: Acute Glomerular Nephritis with Special Reference to the Course and Prognosis, J. A. M. A. **111**:668 (Aug. 20) 1938.

3. I have personal knowledge of only the children seen during 1936 and 1937. All information on patients observed prior to this time was obtained from the records of the hospital.

September 1926 and April 1937. The diagnosis was based primarily on the appearance of red blood cells, albumin and casts in the urine. The appearance of edema, hypertension and cerebral manifestations was variable and did not occur in all cases. It is felt that all cases included were cases of true glomerular nephritis.

The children were examined from one to nine years after the original observation. The study consisted of physical examinations, blood pressure determinations, Addis sediment counts on the urine and, whenever possible, urea clearance tests. When abnormalities were discovered the children were examined repeatedly to determine the presence or absence of glomerular nephritis.

TABLE 1.—*Glomerular Nephritis with History of Initial Stage*

	Rochester		Stanford	
	Number	Percentage	Number	Percentage
Lesions healed	76	74.5	44	40
Lesions active	14	13.7	52	47.2
Patient dead	12	11.8	14	12.8
Case not followed	39	....	20	....
Total	141		130	

TABLE 2.—*Glomerular Nephritis (All Cases)*

	Rochester		Stanford	
	Number	Percentage	Number	Percentage
Lesions healed	17	72.6	57	37
Lesions active	15	14.2	64	41.5
Patient dead	14	13.2	33	21.5
Case not followed	40	....	24	....
Total	146		178	

The Rochester and Stanford case have been tabulated so that comparison may be made. It must be remembered that the Stanford survey covers sixteen years and the Rochester study eleven years, so that allowance for the difference in the total number of cases must be made. However, the percentages of the two series afford satisfactory means of comparison.

Seventy-four and five-tenths per cent of the Rochester patients with a history of the initial stage of glomerular nephritis were found to show healing of the lesions, whereas in only 40 per cent of the Stanford cases did healing occur during the same period. Both series show approximately the same mortality, but the cases of still active nephritis at Stanford were far greater in number and percentage (47.2 per cent) than those discovered in Rochester (13.7 per cent).

A comparison of the total number of cases in the two series demonstrates the same high percentage of cases of healed glomerular nephritis in Rochester and a high percentage of cases of the active condition at Stanford (table 2).

TABLE 3.—*"Active" Cases with History of Initial Stage*

	Rochester		Stanford	
	Number	Percentage	Number	Percentage
Over 2 years	5	35.7	27	51.9
Less than 2 years	9	64.3	25	48.1
Total	14		52	

TABLE 4.—*All "Active" Cases*

	Rochester		Stanford	
	Number	Percentage	Number	Percentage
Over 2 years	6	40.0	35	54.6
Less than 2 years	9	60.0	29	45.4
Total	15		64	

TABLE 5.—*Mortality in Cases with Initial Stage*

	Rochester		Stanford	
	Number	Percentage	Number	Percentage
Died from chronic nephritis	2	16.6	7	50
Did not have chronic nephritis	10	83.4	7	50
Total	12		14	

TABLE 6.—*General Mortality*

	Rochester		Stanford	
	Number	Percentage	Number	Percentage
Died from chronic nephritis	4	28.5	26	78.7
Did not have chronic nephritis	10	71.5	7	21.3
Total	14		33	

The number of "active" cases in the two series shows striking dissimilarities. Sixty-four are listed in the Stanford series over a sixteen year period as compared to 15 remaining in the Rochester series over an eleven year period. This is a greater difference than can be explained by the extra five years of the Stanford survey. The percentage of patients with nephritis of more than two years' standing is approximately the same in the two series, but the greater number of cases of the active condition at Stanford is significant.

The number of children that have died also show marked differences in the two series. Thirty-three (21.5 per cent) of the Stanford children died, as compared with 14 (13.2 per cent) of the Rochester children. Twenty-six (78.7 per cent) of the 33 Stanford children died of chronic nephritis, and only 4 (28.5 per cent) of the 14 Rochester children died of this condition. The majority of the Rochester children who died (10, or 71.5 per cent) did not have chronic nephritis but died either during the initial stage (6, or 42 per cent) or of an associated intercurrent infection (4, or 28 per cent). It is of interest to note that 3, or 20 per cent, of the 14 dead in the Rochester series died within the first few days of acute glomerular nephritis with convulsions and myocardial failure and only 1, or 3 per cent, of Stanford patients died of acute nephritis.

The Rochester study does not bear out the gloomy prognosis found in the Stanford study, but the explanation of this disagreement is not clear. It has been suggested that disagreement in the classification of glomerular nephritis, lack of recognition of the latent stage and inaccurate methods of studying the urine were all factors that may have caused discrepancies in statistics on prognosis. These possibilities are eliminated, as the same observer made both studies. The method of treatment played no role, as there was no difference in therapy in the two institutions. The part that Dr. Addis personally played in attracting a greater number of patients with severe and chronic glomerular nephritis to Stanford is difficult to determine. Not only patients with the chronic condition but many patients with acute glomerular nephritis came to his clinic, and a review of the Stanford cases reveals that approximately 40 per cent of the chronically ill patients presented themselves first to the clinic service. Teaching hospitals and medical schools usually act as centers to which patients with difficult or chronic conditions are attracted, and it is to be supposed that the University of Rochester clinic would have attracted its share of such patients from the surrounding territory.

The possibility remains that the clinical picture of nephritis may differ geographically. This phenomenon is difficult to establish from clinical impression alone, but a tabulation of the dead patients and patients with chronically active glomerular nephritis in the two studies demonstrates striking differences which suggest the possibility of a geographic influence (table 7).

The best available index of the prognosis of glomerular nephritis is the percentage of the number of patients who die of the disease plus those with lesions active two years or more. (A two year period is used, as it has been shown that few children recover after having had glomerular nephritis for two years.[1]) Thirty-nine per cent of all the patients in the Stanford group are dead or have had nephritis for two

or more years, as contrasted with only 10.6 per cent of the children in the Rochester series. The higher percentage of dead and chronically nephritic children in the Stanford series is difficult to explain simply on the basis of the greater number of such cases in that hospital. It appears likely that in the Stanford area a greater percentage of children with acute nephritis had chronic nephritis than in the Rochester area. On the other hand, although there are too few cases to draw definite conclusions, it would appear that the Rochester children have a more severe initial stage of glomerular nephritis (to which they may succumb) than was found in the Stanford study. For example: 3 or 20 per cent, of the 14 dead in the Rochester series died within the first few days with convulsions and myocardial failure, whereas only 1, or 3 per cent, of the 33 dead in the Stanford series presented the same picture.

It must be pointed out that a definite source of error exists in the prognostic statistics of these two studies as well as other similar surveys.

TABLE 7.—*Patients Dead or with Lesions Active More than Two Years*

	Rochester			Stanford		
	Total Nephritis Cases	Dead or Active 2 Yr.	Percentage	Total Nephritis Cases	Dead or Active 2 Yr.	Percentage
All cases of nephritis.....	106	10	10.6	154	61	39
Cases with history of initial stage	102	7	7	110	34	30

This possible error is in the determination of the actual onset. Diagnosis of acute initial nephritis is usually made when the clinical symptoms of nephritis first become apparent. However, it has been demonstrated that the initial stage may be subclinical, with no demonstrable edema, hypertension or gross hematuria, and that the classic picture of acute glomerular nephritis may be missing in a high percentage of cases. In fact, many children may have an "insidious onset" or subclinical initial stage several years prior to the first gross hematuria or appearance of edema, and the diagnosis of glomerular nephritis is not made until these later symptoms manifest themselves after an acute infection.[4] How many of the chronically nephritic patients in the Rochester and the Stanford service fall into this category is difficult to say, but it is possible that in the Stanford area the onset of the disease occasions less of a generalized reaction, and there is, as a result, a higher per-

4. A study being completed at present may help in the differentiation of the initial stage from an exacerbation of a preexisting renal lesion. The sedimentation rate is usually found to be markedly elevated during and after the initial stage of glomerular nephritis, whereas it remains virtually unchanged during an exacerbation of chronic nephritis.

centage of children whose disease has had an "insidious onset." These children months or years later would show acute symptoms and would erroneously be considered to be having the initial stage at this later date. The case of Grace W., reported in the previous publication,[1] is an example of this type of latent nephritis.

This type of error may explain the fact that a higher percentage (47.2 per cent) of "active" cases was found in the Stanford series than in Rochester (13.7 per cent) but does not explain the actual greater number of chronically ill children found at Stanford. If the healing of the glomerular nephritis were in direct proportion to the intensity of the disease at the onset as some have suggested, one could explain the greater number of cases of chronic nephritis in the Stanford series by the fact that there were more children in whom the disease had an insidious onset. Neither series presents any proof of this hypothesis, however, as children in whom the disease had an insidious onset have been shown to recover and in others in whom the onset was very acute the process has gone on to a chronic stage.

SUMMARY

A follow-up study of 146 children with glomerular nephritis was made in the children's clinic of the University of Rochester School of Medicine from 1926 to 1937. The results were compared with those of a similar study of 178 cases observed in San Francisco in the Stanford Medical School from 1920 to 1936.

A higher percentage of children recovering from glomerular nephritis was found in the Rochester series.

The percentage of dead and chronically nephritic patients in the Stanford series was much greater than that in the Rochester series. Sampling and a geographic difference in the clinical manifestations of glomerular nephritis are suggested as possible explanations for the differences in the prognosis figures in the two series.

Case Reports

MENINGITIS DUE TO STAPHYLOCOCCUS AUREUS HAEMOLYTICUS TREATED WITH SULFANILAMIDE

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AND
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In reviewing the literature of the septic meningitides, one is impressed by the relatively high mortality. Holt and McIntosh [1] stated that the course of staphylococcic meningitis is usually rapidly progressive and almost invariably terminates in death. However, isolated reports of recovery from staphylococcic meningitis have appeared in the literature at intervals. The occurrence is still sufficiently rare to justify addition of our case to the small series on record.

Schless [2] has given an excellent review of the literature for the period up to 1932. He found instances in which recovery occurred on removal of a focus adjacent to the meninges. Analysis reveals that in the majority of these cases the condition must be considered not as true generalized meningitis but rather as a local process which cleared promptly on surgical intervention. To date (June 1938) only 8 cases of staphylococcic meningitis in which recovery occurred have been reported in the literature.[3] These cases have been summarized in table 1.

From the Department of Otolaryngology, Children's Hospital of Michigan.

1. Holt, L. E., and McIntosh, R.: Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton-Century Company, 1933, p. 1021.

2. Schless, R. A.: Staphyloccocus Aureus Meningitis, Am. J. Dis. Child. **44**:813 (Oct.) 1932.

3. (*a*) Barker, L. F.: Recovery from Staphylococcus Septicaemia with Meningitis, Internat. Clin. **35**:1, 1925. (*b*) Lamb, F. H.: Report of a Case of Staphylococcus Meningitis Treated with Intraventricular Injections of Gentian Violet, Arch. Pediat. **45**:306 (May) 1928. (*c*) Stout, B. F.: Septic Cavernous Sinus Thrombosis: Report of Two Cases with Recovery, J. Lab. & Clin. Med. **17**:28 (Oct.) 1931. (*d*) Dunlap, J. E.: Staphylococcic Meningitis with Recovery, J. A. M. A. **104**:1594 (May 4) 1935. (*e*) Biltz, R. L., and Hermann, E.: Staphylococcic Septicemia with Meningitis and Multiple Abscesses Treated with Gentian Violet Intravenously, J. Med. **17**:247 (July) 1936. (*f*) Jackson, R. L.: Staphylococcus Aureus Meningitis, J. Pediat. **11**:518 (Oct.) 1937. (*g*) Fritz, M., and Hollister, W.: Meningitis Due to Staphylococcus Aureus Haemolyticus, Arch. Otolaryng. **27**:317 (March) 1938. (*h*) Schless.[2]

One previous case of staphylococcic meningitis which was treated with sulfanilamide has been reported by Bloch and Pacella.[4] However, no mention was made of spinal fluid culture or of other significant data on the spinal fluid.

According to the reports, there is some variance between the experimental and the clinical findings regarding the efficacy of sulfanilamide against infection due to Staphylococcus aureus. Long and Bliss [5] concluded from their experiments in vitro that a 1 : 10,000 concentration of sulfanilamide in serum broth had no effect on the growth of Staph.

TABLE 1.—*Summary of Data on Reported Cases of Meningitis Due to Staphylococcus Aureus with Recovery*

Author	Date	Sex	Age, Yr.	Source	Staph. Aureus Cultured in: Spinal Fluid	Staph. Aureus Cultured in: Blood	Treatment	Duration, Wk.
Barker [3a]	1925	M	47	Prostatitis	+	+	?	2
Lamb [3b]	1928	F	1	Obstructive hydrocephalus	+	—	Methylrosaniline (gentian violet), 0.1% solution	2
Stout [3c]	1931	F	16	Furuncle of chin	+	+	Bacteriophage and blood transfusions	11
Schless [2]	1932	M	13	Furuncle of left tibia	+	—	Bacteriophage	3
Dunlap [3d]	1935	M	8	Infected lumbar cyst or tonsillitis	+	—	Bacteriophage and aeriflavine 1:4,000	2½
Biltz and Hermann [3e]	1936	F	7	Infection of upper part of respiratory tract	+	+	Methylrosaniline, 5% solution	2
Jackson [3f]	1937	F	2	Scarlet fever	+	+	Cisternal and lumbar taps, blood transfusions and dextrose given intravenously	3
Fritz and Hollister [3g]	1938	M	13	Mastoiditis	+	—	Staphylococcus antitoxin, sulfanilamide and blood transfusions	2

aureus. Britton [6] found no definite bactericidal or bacteriostatic effect on freshly isolated cultures of either Staph. aureus or Streptococcus haemolyticus with various compounds of sulfanilamide. Experiments of Buttle and his co-workers [7] failed to show any protection in mice

4. Bloch, H., and Pacella, B. L.: Staphylococcic Meningitis, J. A. M. A. **110**:508 (Feb. 12) 1938.

5. Long, P. H., and Bliss, E. A.: Para-Amino-Benzene-Sulfonamide and Its Derivatives, J. A. M. A. **108**:32 (Jan. 2) 1937.

6. Britton, C. J. C.: The Effect of Sulphonamide Compounds on Certain Bacteria in Vitro, Brit. J. Exper. Path. **29**:141 (April) 1938.

7. Buttle, G. A. H.; Gray, W. H., and Stephenson, D.: Protection of Mice Against Streptococcal and Other Infections by p-Aminobenzene-Sulphonamide and Related Substances, Lancet **1**:1286 (June 6) 1936.

against staphylococcic infections, but the strains of staphylococci available necessitated the use of extremely large doses. He also found no protection against large doses of relatively avirulent streptococci.

Despite these reports, Hoerlein [8] stated:

> Prontosil did not prove so specifically effective in staphylococcal infections in mice as in streptococcal infections. On the other hand, it proved to be an effective chemo-therapeutic in staphylococcal infections in rabbits. Noteworthy results have been reported on the continent by its use in staphylococcal infections in man.

REPORT OF A CASE

History.—A. M., a white boy of 4 years, was admitted to the Children's Hospital of Michigan on March 21, 1938, at 12:30 p. m. complaining of a painful, swollen cheek and a discharging ear.

The child had been well until three weeks previous to entry, when he contracted measles. He had a good convalescence until four days prior to admission, when elevation of temperature was noted. The glands of the cervical region became tender and swollen; a sanious nasal discharge developed; the left eyelids became edematous, and the left ear drum spontaneously ruptured. During the two days before the boy's admittance severe backache, general malaise and anorexia were present.

The past history and the family background were irrelevant.

Physical Examination.—Examination revealed a well developed, well nourished white boy of 4 years who was not acutely ill. He showed a chemotic process involving the left eyelids and marked injection of the bulbar conjunctiva. There was no limitation of ocular movements; the pupils were moderately dilated and reacted normally to light. Funduscopic examination revealed normal disks with no involvement of the retinal vessels. Examination of the ears showed a normal-appearing right drum, but the left external canal showed a purulent pulsating discharge. However, there was no tenderness over the mastoid. A purulent discharge was noted in the left naris, with free pus beneath the inferior turbinate. Palpation of the paranasal sinuses revealed tenderness over the left maxilla. The child showed a picture of acute nasopharyngitis, with injected mucosa, hypertrophied tonsils and a purulent postnasal drip. The cervical glands were enlarged, discrete and tender. Examination of the other systems gave essentially negative results. Neurologic study showed no abnormality. The tendon reflexes were active.

Roentgen and Bacteriologic Examinations.—The morning after the patient's admission, roentgen study of the paranasal sinuses and mastoids showed uniform dense opacity of the left antrum and of the left group of ethmoid cells, with associated hypertrophy of the soft tissues of the left naris. The mastoids were of the adult type, with generous cellular development; the left mastoid showed evidences of infiltration but no destruction. Cultures of material taken from the ear and the nose showed Staph. aureus.

Clinical Course.—After local treatment for the acute suppurative sinusitis and otitis media, there was gradual subsidence of symptoms until the seventh day,

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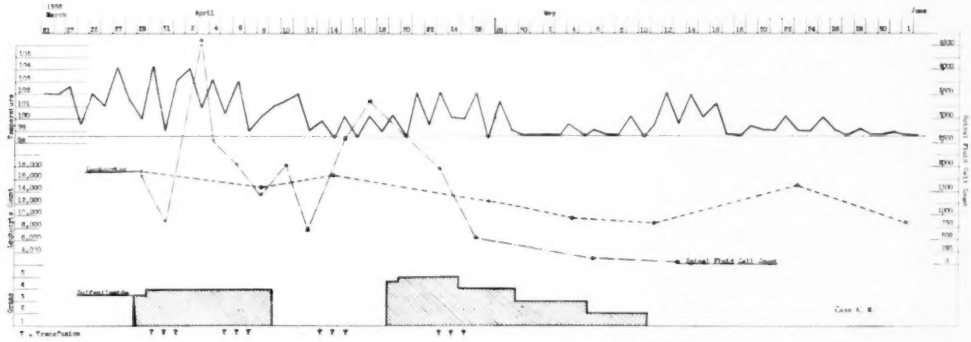
8. Hoerlein, H.: Development of Chemotherapy for Bacterial Diseases, Practitioner **139**:635 (Dec.) 1937.

when the tenderness over the left mastoid became pronounced. A check-up roentgen study of the mastoid showed a definite increase in the amount of infiltration, with some destruction on the left. Invasive symptoms were noted as the temperature became elevated to 104 F. On the evening of the eighth day the boy evidenced signs of meningeal irritation, with severe frontal headache and lancinating retrobulbar pain on the right. Nuchal rigidity was noted, and Kernig's sign was present. Lumbar puncture on March 29 yielded cloudy fluid with 1,580 cells per cubic millimeter, of which 87 per cent were polymorphonuclears. Pandy's test gave a positive reaction (4 plus); the sugar content was 29 mg. and the protein content 56 mg. per hundred cubic centimeters under normal pressure. Examination of the centrifuged spinal fluid revealed no organisms. The blood contained 9.6 Gm. of hemoglobin per hundred cubic centimeters (Sahli); there were 3,850,000 red cells and 17,500 white cells per cubic millimeter, of which 82 per cent were polymorphonuclears, 16 per cent lymphocytes and 2 per cent mononuclears. Early exenteration of the mastoid with adequate dural exposure was considered urgent in view of the development of meningitis accompanied by a fulminating type of mastoiditis.



Course of meningitis due to Staph. aureus haemolyticus in a 4 year old boy (A. M.).

Operation: On March 29, the day of operation, the patient was given 300 cc. of a physiologic solution of sodium chloride containing 5 per cent dextrose by intravenous injection before a complete mastoidectomy. This was performed with the child under nitrous oxide and oxygen anesthesia. Considerable destruction was encountered near the antrum and the horizontal semicircular plate; the carious process extended down to the tegmen tympani but did not involve the inner table. The dura, which was uncovered from the sinus-dural angle to the zygomatic root, had a normal appearance, no granulations or hyperemia being noted. Cultures of material taken from the mastoid yielded Staph. aureus and nonhemolytic streptococci.

Postoperative Course: The patient's condition remained critical after the operation. He was given three small blood transfusions (125 cc. of citrated blood), and fluids (300 cc. of a 5 per cent solution of dextrose in distilled water) were administered parenterally twice a day. Despite the fact that spinal fluid culture was reported to be negative at this time, sulfanilamide therapy was started. Lumbar puncture on March 31 showed 620 cells per cubic millimeter, 82 per cent of which were polymorphonuclears; Pandy's test gave a 2 plus reaction; the

sugar content was 16.2 mg. and the sulfanilamide level 8.1 mg. per hundred cubic centimeters. Cultures on nutrient broth and chocolate agar showed Staph. aureus haemolyticus.

During the ensuing week the patient remained in a stuporous condition. The neck remained rigid, and marked cyanosis of the lips and nail beds was noted. Parenteral administration of fluids, interstitial injection of sulfanilamide and blood transfusions were continued, as shown in the accompanying chart. To preclude contamination, the spinal fluid was plated with chocolate agar; the resulting growth showed a uniform distribution of colonies of Staph. aureus haemolyticus.

TABLE 2.—*Laboratory Data in the Case of A. M.*

	Spinal Fluid							Sulfanilamide Levels, Mg. per 100 Cc.	
Date, 1938	No. of Cells per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Pandy Test	Sugar, Mg. per 100 Cc.	Protein, Mg. per 100 Cc.	Cultures*	Spinal Fluid	Blood
3/29	1,580	87	13	++++	29.0	56	Negative (5 days)	...	....
3/31	620	82	18	++	16.2	...	Staph. aureus haemolyticus	8.1	....
4/ 1	...	..	..	....	....	...	.....	...	15.0
4/ 2	4,600	90	10	++++	15.0	120	Staph. aureus haemolyticus	1.0	7.6
4/ 4	2,750	86	14	++++	....	120	Staph. aureus haemolyticus	10.5	17.0
4/ 6	2,090	85	15	++++	18.0	138	Staph. aureus haemolyticus	13.8	19.0
4/ 8	1,400	88	12	++++	27.0	106	Staph. aureus haemolyticus	13.6	....
4/10	1,850	90	10	++++	20.0	106	Staph. aureus haemolyticus	2.4	....
4/12	620	45	55	++++	20.0	67	Staph. aureus haemolyticus	....	....
4/15	2,450	80	20	++++	21.0	50	Staph. aureus haemolyticus	....	....
4/19	3,280	70	30	++++	41.0	152	Staph. aureus haemolyticus	....	....
4/23	1,950	75	25	++++	11.5	225	Staph. aureus haemolyticus	....	....
4/26	520	40	60	++++	....	...	Staph. aureus haemolyticus	12.0	....
4/29	400	30	70	++++	7.0	87	Staph. aureus haemolyticus	10.2	....
5/ 6	92	20	80	++++	47.0	112	Negative (5 days)	4.4	....
5/13	39	35	65	++	52.0	64	Negative (5 days)	...	....

* Cultures were made on nutrient broth and chocolate agar.

Culture of blood taken on April 1 was reported as positive for Staph. aureus. Spinal fluid obtained by lumbar puncture on April 2 showed 4,600 cells per cubic millimeter, 90 per cent of which were polymorphonuclears; Pandy's test gave a 4 plus reaction; there were 15 mg. of sugar and 120 mg. of protein per hundred cubic centimeters. Culture yielded Staph. aureus haemolyticus.

Lumbar punctures repeated on alternate days (table 2) continued to show an elevated cell count, a decrease in sugar content and an increase in the protein level. Cultures continued to yield Staph. aureus haemolyticus.

On April 8 the blood contained 8.5 Gm. of hemoglobin, 3,670,000 red cells and 15,100 white cells, with 84 per cent polymorphonuclears and 16 per cent lymphocytes. On the following day the child had a severe chill accompanied by marked cyanosis and repeated emesis. Since no great change in the spinal fluid or the

clinical status was noted with the administration of sulfanilamide, it was discontinued at this time. After the interruption of the drug, the patient seemed more alert, but nuchal rigidity remained, and horizontal nystagmus developed. The temperature curve, which previously had a picket fence character, tended to flatten out.

During the next few days improvement continued; the patient was able to sit up and take fluids. Parenteral administration of fluids, which had been given since the ninth day, was discontinued. However, the child's improvement lasted only a week. On April 16 the blood contained 11.8 Gm. of hemoglobin, 4,450,000 red cells and 17,200 white cells, of which polymorphonuclears comprised 86 per cent, lymphocytes 12 per cent and mononuclears 2 per cent. Lumbar puncture on April 19 showed an increase in cells to 3,280, 70 per cent of which were polymorphonuclears, and cultures continued to yield Staph. aureus haemolyticus. There was clinical exacerbation with this increased abnormality of the spinal fluid. Since there was little else to offer in the way of treatment, sulfanilamide therapy was resumed. One gram of sulfanilamide in 125 cc. of a physiologic solution of sodium chloride with 6 cc. of lactate-Ringer (Hartmann's) solution was administered interstitially every six hours.

The patient showed some clinical improvement. The neck became flaccid; Kernig's and Brudzinski's signs disappeared. Spinal fluid cell counts gradually assumed more normal values, but cultures remained positive until May 6 (the forty-seventh day). The dose of sulfanilamide was gradually reduced (table 1), and the drug was given orally when vomiting ceased. The temperature curve flattened out, only to have some elevation when the sulfanilamide was finally discontinued, on May 10 (fifty-first day). In view of the slight secondary anemia and the anorexia, administration of a liver extract was started.

Two minor periods of meningeal irritation were accompanied by persistent vomiting. On May 12 the blood contained 11.4 Gm. of hemoglobin, 3,800,000 red cells and 9,600 white cells, of which polymorphonuclears comprised 76 per cent, lymphocytes 23 per cent and monocytes 1 per cent. Clinical improvement continued, and the patient was discharged from the hospital on June 1 (seventy-fourth day). At that time the blood contained 12 Gm. of hemoglobin, 4,240,000 red cells and 9,000 white cells, of which 40 per cent were polymorphonuclears and 60 per cent lymphocytes.

The patient, who was subsequently followed in the outpatient department, showed gradual resumption of the normal activities of childhood. The blood count on June 16 revealed 13 Gm. of hemoglobin, 4,000,000 red cells and 10,500 white cells, of which 64 per cent were polymorphonuclears and 36 per cent lymphocytes. Examination after two months revealed no neurologic changes attributable to the disease.

SUMMARY AND CONCLUSIONS

In this case of meningitis due to Staph. aureus haemolyticus the probable source of infection was either in the mastoid or in the paranasal sinuses. Cultures of material from the nose and mastoid and of the blood and the spinal fluid were repeatedly positive for the organism. Recovery followed mastoidectomy, prolonged sulfanilamide therapy, repeated blood transfusions and parenteral administration of fluids.

Sulfanilamide was given with the approximate daily dose of 1 grain (0.06 Gm.) per pound (0.5 Kg.) of body weight. It was given orally

with equal parts of sodium bicarbonate; when parenteral administration became necessary, it was given in a physiologic solution of sodium chloride with lactate-Ringer (Hartmann's solution) in an effort to decrease acidosis. Sulfanilamide levels in the blood and spinal fluid were determined according to the method of Marshall and his associates.[9]

Totals of 91.9 Gm. of sulfanilamide, 1,500 cc. of citrated blood, 20,975 cc. of parenterally administered fluids, 55 Gm. of sodium bicarbonate and 218 cc. of lactate-Ringer (Hartmann's) solution were given to this patient. Spinal fluid cultures became negative on the forty-sixth day.

It would be difficult to estimate the value of sulfanilamide from observation of this single case of meningitis due to Staph. aureus haemolyticus; yet the clinical impression was favorable. After the first administration of sulfanilamide, the spinal fluid cell count was diminished, but no great improvement occurred. When the drug was discontinued, the cell count became elevated again. On resumption of the sulfanilamide therapy, however, the cells were depleted, and the sugar and protein values assumed a more normal relationship. No untoward results attributable to the sulfanilamide were noted, aside from cyanosis; no hemolytic or agranulocytic anemia developed.

In evaluating this case, the worth of repeated lumbar drainage and of frequent transfusion of small amounts of blood is not to be underestimated.

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CLINICALLY MANIFEST TUBERCULOUS PERICARDITIS

REPORT OF A CASE WITH OBSERVATIONS ON CIRCULATORY CHANGES

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Tuberculosis of the pericardium is not an unusual observation at necropsy,[1] particularly in cases of advanced disseminated tuberculosis; but the presence of clinically manifest, or clinically primary, tuberculous pericarditis is unusual in adults and rare in children.[2] Recognition of this lesion during life has led to a small number of observations on the effects of increased intrapericardial pressure on various circulatory phenomena;[3] that these phenomena are sometimes peculiar and not altogether in accord with those produced by experimental cardiac tamponade [4] is understandable when one keeps in mind that the patho-

From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University, and the Babies Hospital.

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3. (*a*) Thomas, G. W.: Tuberculous Pericarditis Treated with Pneumopericardium, Am. Heart J. **7**:771, 1932. (*b*) Babcock, W. W.: Tuberculous Pericarditis with Enormous Effusion: Pericardiotomy, S. Clin. North America **14**: 39, 1934. (*c*) Coughey, J. L.: A Case of Tuberculous Pericarditis with Effusion: Studies of Venous Pressure Changes, Bull. New York Acad. Med. **13**:11, 1937. (*d*) Stewart, H. J.; Crane, N. F., and Dietrick, J. E.: Recurrent Pericardial Effusion of Unknown Etiology: Report of a Case with Studies of the Circulation and of Absorption from the Pericardial Cavity, ibid. **13**:44, 1937.

4. Bay, E. B.; Gordon, W., and Adams, W.: Blood Pressure and Electrocardiographic Changes in Experimental Pericardial Effusion, Am. Heart J. **8**:525, 1933. Williamson, C. S., and Etts, H. N.: Rationale of Therapeutic Puncture in Pericardial Effusions: An Experimental Study, Arch. Int. Med. **38**:206 (Aug.) 1926. Drinker, C. K., and Field, M. E.: Absorption from the Pericardial Cavity, J. Exper. Med. **53**:143, 1931. Scott, R. W.; Katz, L. N., and Feil, H. S.: Electrocardiographic Changes in Pericardial Effusion, Am. Heart J. **5**:77, 1929.

logic changes in the visceral and parietal pericardial membranes complicate the physiologic alterations produced by excess pericardial fluid alone. The majority of writers have felt that the most satisfactory treatment for this condition, in addition to the familiar measures used against any active tuberculous infection, consists of paracenteses, performed as frequently as necessary for the relief of cardiac compression, followed by the induction of artificial pneumopericardium in order to furnish a more compressible cushion between the heart and the pericardial sac and to lessen the likelihood of the formation of pericardial adhesions. The introduction of air in some cases seems to have retarded the rate of reaccumulation of pericardial exudate.[5] The use of this mode of therapy for a patient studied recently has afforded the opportunity to record some of the effects produced by changes in pressure around the heart.

Determinations of venous pressure were carried out according to the direct method of Moritz and von Tabora,[6] with the apparatus which was used to determine normal values in a series of healthy children recently reported on by Lambert.[7] Intrapericardial pressures were measured directly by means of a manometer connected to the aspirating needle by a three way stopcock. Circulation times (arm to tongue) were determined after the intravenous injection of a saturated solution of saccharin, as described by Fishberg, Hitzig and King.[8]

REPORT OF A CASE

K. B., a 10 year old Negro boy, entered the Babies Hospital on Dec. 22, 1937, because of fever, shortness of breath and abdominal pain. The family history contained no information relevant to the child's illness; in particular, there had been no contact with recognized or suspected active tuberculosis. An older sister was found to have a positive Mantoux reaction; but she showed no evidence of active tuberculosis, and roentgen study of her chest revealed no abnormal features. Since 1931, when she was hospitalized for pneumonia and pleurisy due to Pneumococcus type I, she had been entirely well. Clinical examination, a tuberculin

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test and roentgen study of the thorax disclosed no evidence of tuberculosis in the other members of the family.

Except for infrequent infections of the upper part of the respiratory tract and an attack of suspected pneumonia at the age of 3 years (for which he was not hospitalized), the patient had always been considered well. About four months before coming to the hospital he sustained a severe bruise of the midsternal region of his chest, when a high stool on which he stood collapsed in such a way that he was thrown forward, striking his chest directly on the sharp corner of a rigid table. The injured area turned black and blue, and for several days the boy seemed feverish and complained of severe, though poorly localized, pains in his chest. As this episode subsided, he seemed entirely well; he had no complaint until almost three months later, when he became conscious of substernal pain, described as "like pins and needles." When examined by the family physician he was found to have fever and a rapid pulse and was advised to remain in bed. This he did; during the next three weeks no new symptoms appeared, but the pain remained constant, and the temperature rose to 101 or 102 F. daily. Rather suddenly, five days before the child came to the hospital, the substernal pain disappeared; the boy became more feverish, complained of crampy pain in the lower part of the abdomen, vomited frequently and seemed extremely ill. Swelling of the legs, scrotum and abdomen was noted; the breathing became labored, and the lips "turned blue."

Examination showed an alert, cooperative, well developed and well nourished boy with marked dyspnea, orthopnea and cyanosis and considerable edema of the dependent parts. The temperature was 104 F., the pulse rate 160, the respiratory rate 48 and the blood pressure 100 mm. of mercury systolic and 70 mm. diastolic. The veins of the optic fundi and of the neck were full. The cardiac dulness was greatly increased in all diameters, and no apical impulse could be detected; the sounds were rapid and muffled, but neither murmur nor friction rub was heard. There was diminished resonance, with numerous moist squeaky rales over the entire left side of the thorax except in the area below the scapular spine, where there were tympany, bronchovesicular breath sounds and egophony. The pulmonary field on the right seemed clear, with moderate hyperresonance and roughened breath sounds. The abdomen was distended and tense, with dulness in the flanks and a greatly enlarged tender liver, which extended to the iliac crest; the spleen could not be identified, but there was a suggestion of an indistinct tender mass in the left upper quadrant. No fluid wave was elicited. The peripheral pulse was weak and paradoxic, fading completely on inspiration.

The hemoglobin concentration was 13.3 Gm. per hundred cubic centimeters (78 per cent, Sahli) and the erythrocyte count 4,000,000 per cubic millimeter. There were 11,000 leukocytes per cubic millimeter, with 74 per cent polymorphonuclear cells, 23 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. Urinalysis showed no pathologic condition. The erythrocyte sedimentation rate (Westergren) was 17 mm. in a half-hour and 41 mm. in an hour; the serum antistreptocolysin titer was 250 units. The venous pressure was 200 mm. of water and the circulation time 20.5 seconds. Roentgen study of the chest demonstrated a greatly enlarged cardiac shadow (fig. 1).

Massive pericardial effusion seemed obvious; the cause of the condition could not be definitely established because posterior paracentesis, which was attempted at the time of the patient's admission, yielded no fluid. During the next two weeks there was little change in the boy's condition; fever and disproportionate

tachycardia continued, and there was slight subjective improvement under hospital care. Attempts to produce diuresis by the use of ammonium chloride followed by mercurin suppositories failed. In spite of the failure of paracentesis, the existence of a large effusion was not doubted, and additional data suggested a tuberculous cause: The Mantoux reaction was positive, blood cultures remained sterile, the serum antistreptocolysin titer failed to rise above 250 units, and cultures of material from the nose and throat yielded a varied flora, including Staphylococcus aureus haemolyticus, Streptococcus viridans, Micrococcus catarrhalis and a few pneumococci. The hemoglobin level rose to 16.2 Gm. (95 per cent) and the erythrocyte count to 4,590,000, while the erythrocyte sedimentation rate fell to 8 mm. in a half-hour and 18 mm. in an hour; the leukocyte count

Fig. 1.—Roentgenogram of the chest made at the time of the patient's admission.

was reduced to 8,000, the differential count remaining essentially unchanged. The patient had no productive cough or sputum; pooled and concentrated stomach washings showed no acid-fast organisms, and cultures of this material subsequently yielded no growth on Frobisher's medium.

A second paracentesis was then attempted, and this time only 10 cc. of serosanguineous fluid was secured; it contained 61,000 red blood cells and 1,050 leukocytes per cubic millimeter; there were 37 per cent polymorphonuclear cells, 58 per cent lymphocytes and 5 per cent eosinophils. Routine cultures remained sterile; no tubercle bacilli were seen on direct smears or grown on Frobisher's medium. As the patient's condition grew more alarming and as little relief was afforded by an oxygen tent or by attempted digitalization, a third paracentesis was done, four days later; this time 375 cc. of fluid similar to that previously withdrawn was obtained from a site just lateral to and below the left nipple.

Immediate subjective improvement was accompanied by decrease in pulse rate, increase in pulse pressure and loss of the paradoxic quality. One hundred cubic centimeters of air was then injected, and roentgenograms were made with the patient in various positions (fig. 2). These showed a greatly thickened parietal pericardium, considerable residual pericardial fluid, no adhesions between the pericardial surfaces, a cardiothoracic index of 0.53 and a pericardiothoracic index of 0.81. Again no tubercle bacilli were demonstrated, either by direct smear or by culture of the centrifuged sediment. On the day following this first successful paracentesis the venous pressure was 40 mm. of water—well within normal limits; the circulation time had risen, insignificantly, to 23.5 seconds. The change in circulation time may have been due to the injection of a smaller amount of saccharin than had been used previously, though subsequent determinations showed

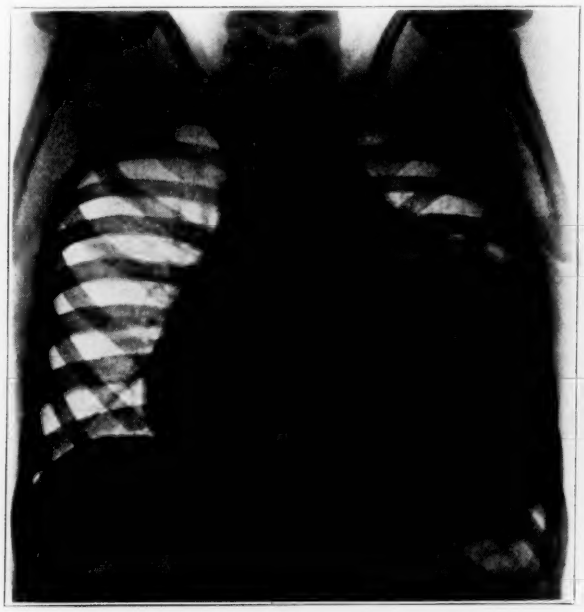

Fig. 2.—Appearance after the removal of 375 cc. of pericardial fluid and the introduction of 100 cc. of air.

a narrow though constantly elevated range of 19.9 to 23.5 seconds, without any significant variation in relation to the amount of pericardial fluid present or the time of its removal.

Eight subsequent paracenteses were carried out during the next fourteen weeks, the procedure being done whenever indicated by increase in the signs of cardiac compression; on each occasion as much fluid as possible was removed, the amounts ranging up to 650 cc. After each tap, from 200 to 400 cc. of air was injected (fig. 3). The fluid gradually became more serous, contained from 58 to 94 per cent polymorphonuclear cells and varied in specific gravity from 1.018 to 1.021. Despite the early failures, acid-fast organisms were easily observed in the centrifuged sediment in each one of these specimens; a typical growth of Mycobacterium tuberculosis was always secured on Frobisher's medium, and in 2 inoculated guinea pigs tuberculosis developed.

As the disease progressed, relief from paracentesis became progressively less gratifying, and all of the classic signs of congestive heart failure increased. With greater enlargement of the liver, icterus appeared during the second month of the patient's illness and increased slowly, the serum bilirubin reaching a final level of 6.4 mg. per hundred cubic centimeters, of which 4.1 mg. gave the direct van den Bergh reaction. The hepatic odor of the breath became pronounced. Increasing edema was reflected by a gain of about 7 Kg. in the last month of life. While the hemoglobin level rose to 19.4 Gm. per hundred cubic centimeters (114 per cent) and the red blood cell count to 5,500,000 per cubic millimeter, the erythrocyte sedimentation rate fell to a final level of 2 mm. in an hour. Throughout the patient's hospitalization the leukocyte counts showed only slight variation, ranging between 7,400 and 11,900 per cubic millimeter, with from 60 to 84 per

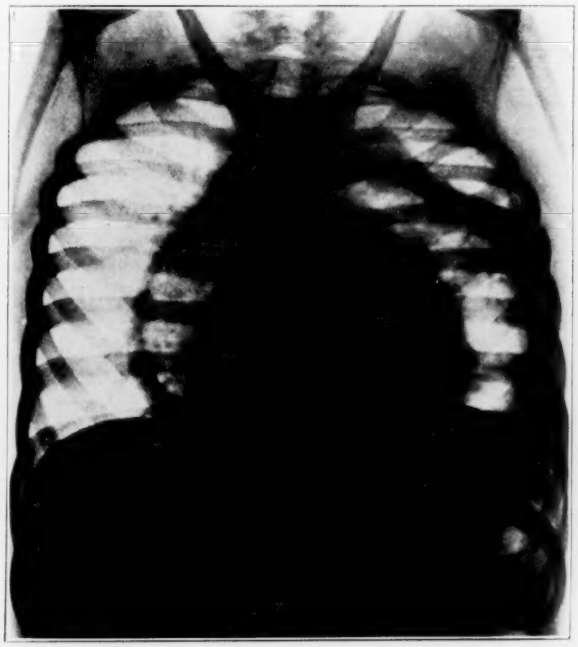

Fig. 3.—Maximal pneumopericardium after practically complete aspiration of pericardial exudate. Note that the cardiac shadow is normal in size, shape and position and that the pericardial sac is greatly dilated and thickened; signs of pleural involvement are present on the left.

cent polymorphonuclear cells; there were no significant changes in the proportions of other types of white blood cells. Numerous urinalyses showed a normally variable specific gravity, albuminuria in amounts ranging from traces to 2 plus, an occasional positive reaction with the benzidine test, and microscopic hematuria and pyuria in several specimens; a small number of hyaline and finely granular casts were seen. Pooled and concentrated sediment from 9 twenty-four hour collections of urine yielded no acid-fast organisms on smear or culture. The question of amyloidosis was raised because of the persistent albuminuria and the incidental roentgen finding of considerably enlarged renal shadows. A congo red

test was done, and 75 per cent of the dye injected intravenously was recovered in one hour, as compared with 94 per cent from the control subject. The total serum protein, as well as the albumin and globulin fractions, determined on four occasions during the latter half of the illness, remained in the low normal or "critical" range and probably constituted another factor in formation of edema. The character of the stools never suggested the presence of gastrointestinal tuberculosis; several examinations failed to show the presence of occult blood, and about six weeks prior to the patient's death roentgen visualization of a barium sulfate meal showed no abnormalities.

In addition to the signs just mentioned, increasingly unfavorable response to paracentesis was evidenced by a steady decline in the systolic blood pressure and the pulse pressure; in the last two months of illness the pulse was continually paradoxic and frequently too weak and rapid to count at the wrist. Oscillometric readings taken in the upper part of the arm in the last week of life showed a maximum excursion of 0.8 at a cuff pressure of 80 mm. of mercury (minimal normal approximately 3). Even with the removal of as much pericardial fluid as could be obtained by aspiration and replacement with air, the venous pressure could not be reduced to the normal range. Frequent electrocardiographic tracings showed changes which appeared to have no direct relation to the amount of pericardial fluid but seemed rather to be due to alterations in the myocardium. There was persistent sinus tachycardia; the PR interval remained constant at 0.11 to 0.12 second, and there was a tendency to low voltage. At one time a moderate degree of left preponderance appeared and at another a change in the level of the ST segment. Inverted or isoelectric T waves were noted, particularly in leads I, II and IVF.

Continuous activity of the tuberculous process was suggested by the persistent irregular fever and proved by the ease with which tubercle bacilli could be recovered from the pericardial exudate. It is interesting that no tuberculous lesions occurred along the tract most frequently pierced by the needle in removing this infected fluid.

Some of the previously cited observations made during the patient's hospitalization are included in figure 4. Simultaneous observations on the relation between the venous and the pericardial pressures (fig. 5*A*) were made on three occasions, showing each time a gradual fall in venous pressure from a greatly elevated initial level to a point still considerably above the normal, with a more abrupt fall in the pericardial pressure from a level slightly lower than the concurrent venous pressure practically to zero. Because of technical difficulties the final pericardial pressures could not be accurately recorded; at each of these paracenteses all of the fluid was apparently removed. After the seventh paracentesis, an increasingly rapid fall in the pericardial pressure was noted with each successive tap (fig. 5*B*); this suggested progressive thickening and loss of elasticity of the pericardial sac. The space from which pericardial fluid could be aspirated seemed to be narrowing with each paracentesis, presumably because of thickening of the shaggy exudate on the pericardial surfaces. Roentgen study showed no increase in the width of the parietal pericardium but did reveal definite enlargement of the cardiac shadow itself (fig. 6), which indicated cardiac hypertrophy, cardiac dilatation or thickening of the visceral pericardium, singly or in combination. Increase in the ascites, development of bilateral hydrothorax (ushered in by typical pleural pain and a fibrinous rub) and failure to ameliorate other manifestations of circulatory failure by the removal of pericardial fluid indicated that the greatest mechanical factor

at play was constriction of the heart and of the great vessels by the organizing visceral pericardial exudate.

In the hope that some relief from cardiac compression might be attained, exploratory pericardiectomy was attempted with the patient under intratracheal cyclopropane anesthesia. The child died during this procedure. A greatly distended and thickened pericardial sac containing a large amount of air and sanguineous fluid was encountered. The serous surface of both the parietal pericardium and the epicardium was covered with shaggy fibrinous exudate, which appeared to be especially abundant on the right side in the region of the great vessels. The

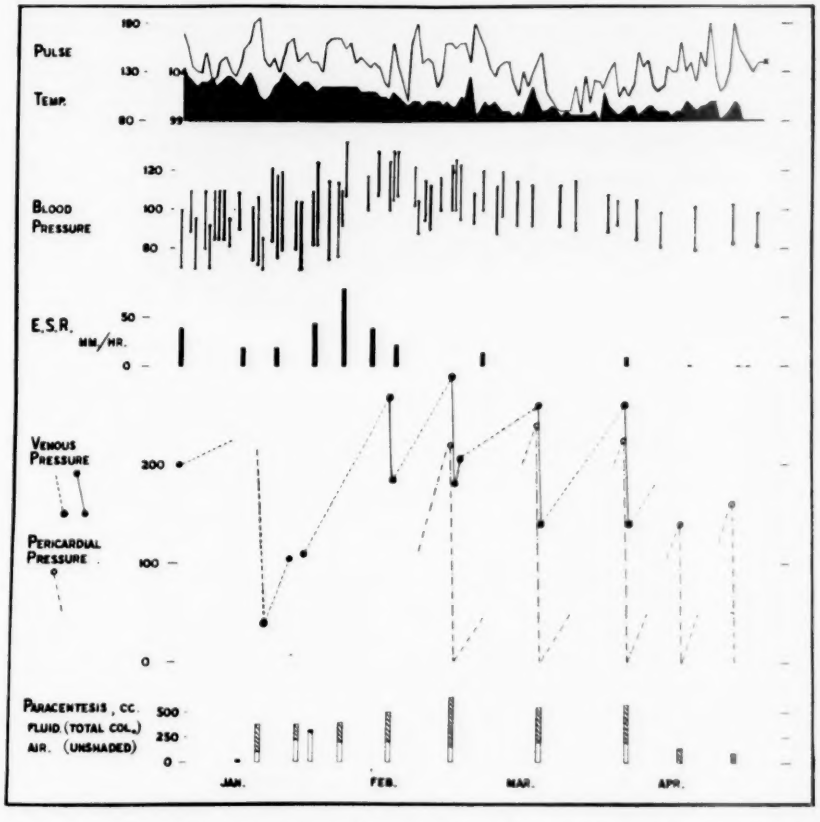

Fig. 4.—Chart illustrating persistent tachycardia and fever, slowly declining systolic blood pressure and pulse pressure, decrease in the rate of erythrocyte sedimentation and the relation of the venous and the pericardial pressure.

exudate was friable superficially; but the deeper layers appeared to be organizing, and it was impossible to establish a plane of cleavage between the exudate and the epicardium. The heart appeared to be dilated, and no adhesions to the parietal surface of the pericardium were discovered at any point.

Pathologic Report.—The pertinent postmortem and microscopic observations can be summarized briefly. The pericardial sac was enlarged and firmly adherent to the anterior thoracic wall, the diaphragm and the medial surfaces of both lungs. From the anterior surface of the sac a portion 8.5 by 5 cm. in area had been

removed at operation. The parietal pericardium was almost cartilaginous in consistence and was thickened to a width of 5 mm. by organizing tuberculous granulation tissue covered by dense shaggy hyalinized fibrin (fig. 7). The epicardial surface of the heart was enveloped in similar organizing exudate; between the parietal and the visceral layer of the pericardium adhesions occurred only over the posterior surface of the left ventricle. Constriction of the orifices of the superior and the inferior vena cava was not apparent, and the auricles and the right ventricle appeared of normal size. The left ventricle was slightly dilated. The myocardium of both ventricles was flabby and pale but not hypertrophied; there was no stenosis of any of the valvular orifices, and the

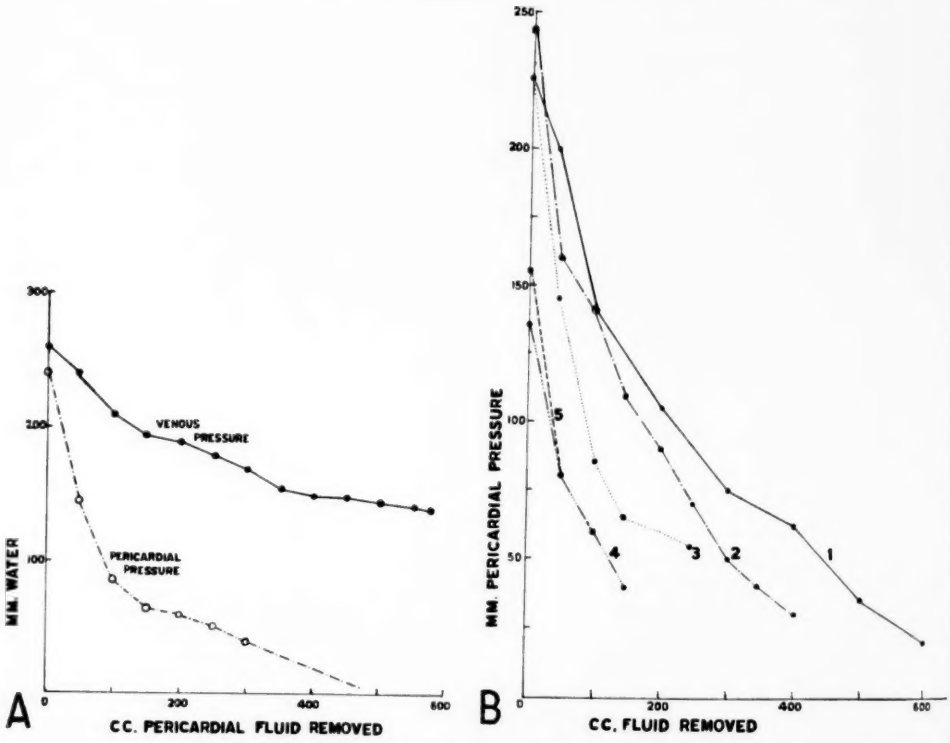

Fig. 5.—*A*, simultaneous record of the venous and the intrapericardial pressure during a single paracentesis. *B*, curves showing increasing rapidity of fall in the intrapericardial pressures with successive paracenteses.

leaflets of the four valves were free from vegetations. Portions of the endocardium of both ventricles were thickened, and polypoid, reddish yellow thrombi, the largest 2 cm. in diameter, were attached to the endocardium of the anterior wall and apex of the left ventricle. A similar thrombus occurred in the right auricle between the musculi pectinati posterior to the opening of the superior vena cava.

The left lung was partially collapsed and was bound to the thoracic wall by fibrous adhesions, between which about 40 cc. of clear fluid had collected. The lung was brownish red and boggy. The right lung was compressed by an accumulation of approximately 600 cc. of fluid in the right pleural cavity; the pleura

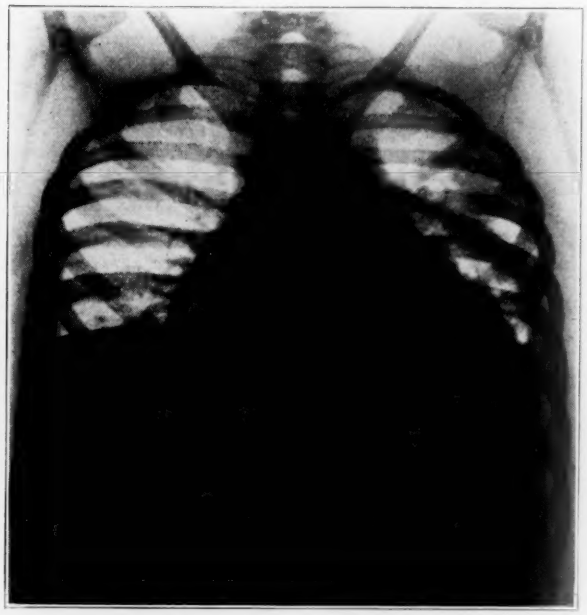

Fig. 6.—Roentgenogram showing persistence of the dilated thickened pericardial sac, but with an increase in the width of the cardiac silhouette; note the bilateral pleural involvement.

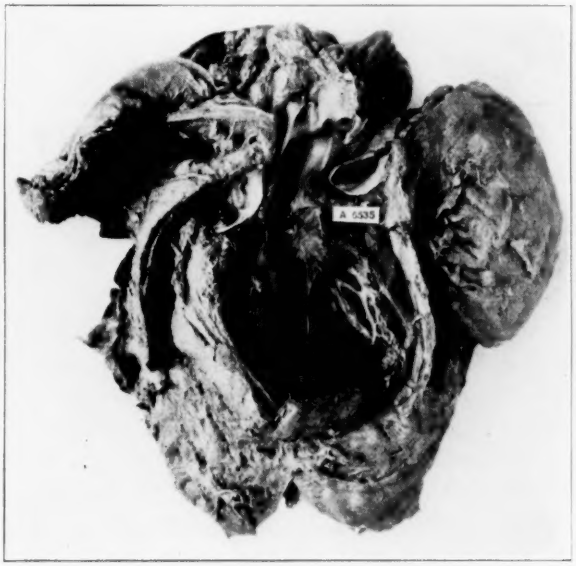

Fig. 7.—Heart with the everted pericardial sac.

was slightly thick and gray but was free from exudate. This lung was similar to the left; in addition the lower lobe contained a recent infarct, and in the upper lobe a scar 7 mm. wide and 15 mm. deep extended from the pleura into the underlying pulmonary parenchyma. There was no microscopic evidence of active or healed tuberculosis in this fibrotic area. At the hilus, inferior to the right main bronchus, one slightly enlarged lymph node contained a small caseous focus.

Immediately posterior to the pericardial sac and between the trachea and the upper lobe of the right lung lay a lymph gland 2 by 1.8 cm. in size which had undergone extensive caseation, calcification and fibrosis. The remaining tracheobronchial nodes were markedly enlarged: Those at the base of the pericardial sac measured up to 3 cm. in diameter, while many of the glands anterior to and at the bifurcation of the trachea were only slightly smaller. These were matted together, but on section individual nodes appeared discrete. Microscopically they showed sclerotic tubercles without necrosis or areas of fibrosis. No tuberculous lesions were discovered in other viscera.

Gross or microscopic evidence of chronic passive congestion was present in the lungs, liver, spleen, pancreas and gastrointestinal tract, and the liver was deeply bile stained. The peritoneal cavity contained about 40 cc. of clear fluid, and portions of the peritoneum were mildly thickened or congested, but chronic perihepatitis and perisplenitis were lacking. Both kidneys were moderately enlarged; in the left was one large depressed infarct, and in the right appeared four healing infarcts of varying size. At the base of one of the infarctions an organized canalized thrombus was demonstrable. No amyloid was noted in any of the viscera.

COMMENT

It is interesting to speculate on the probable course of the infection in this case. Perhaps the most likely assumption is that the "pneumonia" which occurred at the age of 3 years was in reality the primary tuberculous infection, which subsided uneventfully, leaving quiescent parenchymal and tracheobronchial foci which were never recognized. The sharp blow to the chest sustained four months before the patient's admission to the hospital may have been responsible for reactivation of the mediastinal lesion, leading to direct or lymphatic extension of tuberculosis into the pericardial sac, with resultant fibrinous pericarditis and finally massive effusion. The actual point of invasion could not be determined pathologically because of the extensive changes in the pericardial surfaces.

The prominent abdominal symptoms in the early part of the illness were probably due largely to vagal stimulation by the distending pericardial sac and to renal infarctions, the latter accounting also for the urinary changes. The presence of thrombi and infarcts was not suspected clinically, though the symptoms and signs they caused seem characteristic in retrospect. No reason for their occurrence could be made out from a study of the pathologic specimens; in 1 previous case of tuberculous pericarditis, thrombi were apparently caused by direct extension of the infection through the myocardium.

In the literature are reported certain cases of pericarditis with effusion in which the tuberculous etiology was suspected but unproved; many authors have remarked on the difficulty of identifying the organisms in the pericardial exudate of patients subsequently proved to be tuberculous. The early failure to find acid-fast organisms in the present case reemphasizes this difficulty, the need for repeated attempts at proving the diagnosis and the apparent paucity or lack of organisms in the earlier stages of the effusion. One could perhaps justly fear that the frequent sudden changes in pressure relationships incidental to repeated paracenteses enhance the activity of the tuberculous process in the pericardial surfaces, but this risk seems necessary if earlier death from circulatory stasis is to be avoided. Perhaps the use of pericardiotomy for continuous drainage over a longer period—analogous to the siphon treatment of empyema—would be of value after preliminary studies had demonstrated some rigidity of the pericardial sac; this conjecture is given some support by a case reported by Babcock.[3b] Such a procedure would seem worth trying, in view of the prevailing high mortality with the present methods of treatment.

SUMMARY

A case of clinically primary tuberculous pericarditis is presented. Observations on some of the effects produced by increased intrapericardial pressure were made. This disease is rare in children, and its treatment at present is unsatisfactory.

ACUTE DEGENERATION (NECROSIS) OF THE LIVER

REPORT OF A CASE IN A NEWBORN INFANT

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Acute degeneration or necrosis of the liver is a relatively infrequent condition at any age and is extremely rare in early infancy. It is most commonly designated as acute yellow atrophy, a term which is a misnomer and is neither explanatory nor descriptive of the condition, which is not atrophy but necrosis. Other synonyms which have been used are the following: icterus gravis, malignant jaundice, acute parenchymatous hepatitis and parenchymatous degeneration of the liver. The designation acute degeneration of the liver or acute necrosis of the liver seems the most appropriate.

The condition was first described about the sixteenth century. It has been estimated that in about 50 per cent of all cases it occurs in the third decade and in 80 per cent between the ages of 10 and 40 years. Rolleston and McNee [1] in 1929 collected 42 cases in which it occurred in children under 10 years of age. To this group Amberg [2] in 1936 added 14 cases. Among children Phillips [3] found approximately twice as many boys afflicted as girls; this ratio is reversed for adults. The case described by Politzer [4] is one of the earliest recorded and the patient is one of the youngest, a female child who became ill on the fourth day and died on the eighteenth day of life, with all the typical postmortem evidence of the condition. Skormin [5] collected 7 cases in which the condition occurred in newborn infants.

The cause of the condition remains obscure, and despite the many possible causes which have been suggested it usually develops without

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From the Department of Pathology, the University of Minnesota.

1. Rolleston, H. D., and McNee, J. W.: Diseases of the Liver, Gallbladder and Bile-Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 614.

2. Amberg, S.: Diseases of the Liver and Biliary Tract, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 11, p. 39.

3. Phillips, J.: Acute Yellow Atrophy of the Liver in Children, with Report of a Case, Am. J. M. Sc. **143**:177-185 (Feb.) 1912.

4. Politzer, cited by Phillips.[3]

5. Skormin, cited by Rolleston and McNee.[1]

clearcut evidence of the causative agent. Children are not subject to most of the causes reported for adults; however, there are some exceptions. Necrosis of the liver has been found associated with or following acute infectious diseases and sepsis. Arsenical compounds given for congenital syphilis have been held responsible. Phosphorus poisoning, occasionally seen in children, produces rapidly fatal necrosis. Amberg cited the case of a 17 month old infant in whom the condition followed severe burns.

Price [6] in studying hepatic lesions in newborn infants found the severe lesions most frequently when the mother had been treated with barbiturate medication or rectal analgesia. Although in none of his cases was the hepatic lesion the primary cause of death or of such extensive necrosis as is being considered here, the possible deleterious effect on the newborn infant of medication given to the mother before and during labor must be borne in mind.

The disease may be acute, subacute or chronic (healing), and the clinical picture varies accordingly. In the acute form there is usually jaundice, which is rapidly progressive, with an associated decrease in the size of the liver. Anorexia, vomiting and cerebral symptoms are common. Episodes of hemorrhage are frequent. Death usually ensues within a few days. The subacute and the chronic form show a less fulminating clinical picture extending over weeks or months, with some instances of recovery.

Laboratory examinations may be of some assistance. The urine is usually scanty, highly colored and of high specific gravity. It shows marked decrease of urea with an increase of ammonia and other nitrogenous substances. Leucine, tyrosine and other amino acids resulting from hepatic destruction are present. The blood shows a prolonged coagulation time and moderate leukocytosis. There is an increase in the amino acid nitrogen content of the blood with a decrease in the fibrinogen and the dextrose content.

The striking feature of the acute form of this condition is the marked reduction in the size and weight of the liver to a half or even a third of its normal proportions. The capsule is wrinkled, and the whole organ appears collapsed. The cut surface has a mottled appearance and an icteric color, which may be reddish in cases of prolonged involvement. Microscopically there is extensive necrosis, only remnants of liver cells being present and the collapsed stroma giving the appearance of increased fibrosis. The less fulminating conditions may show some regeneration, with proliferation of the bile ducts.

Other observations at necropsy include extensive bile staining of all the tissues and organs. Hemorrhages may be found subcutaneously,

6. Price, A. S.: Hepatic Lesions of the Newborn, Surg., Gynec. & Obst. **65**: 748-752 (Dec.) 1937.

intramuscularly, into and from all the mucous membranes and into any of the organs.

The diagnosis may be extremely difficult. A previous or associated illness may divert attention entirely from any pathologic condition of the liver, especially if jaundice is slight or absent or if no change in the size of the liver is apparent. Gay [7] reported a case of the subacute form in a 10 month old girl who showed no jaundice and whose liver was found to be enlarged at necropsy. In the neonatal period must be considered such conditions as congenital anomaly of the bile ducts, erythroblastosis fetalis, simple icterus neonatorum with associated infection and the so-called idiopathic hemorrhagic disease of the newborn. Woolner [8] reported the case of a boy 19 months old; the mother and several persons in the community had had infectious jaundice during the preceding few months. Catarrhal jaundice is now regarded by some as mild necrosis of the liver in which healing and regeneration have been adequate for recovery. Here the cause is likewise unproved, and a causative organism is rarely identified. Acute necrosis due to poisoning may be diagnosed or suspected from the history.

The treatment must remain empiric and symptomatic until the cause is more clearly understood. In cases of known or suspected poisoning an attempt should be made to produce rapid elimination of the toxic substance. Probably the most valuable single measure is the parenteral administration of dextrose in abundant quantities. It has been shown by Davis and Whipple [9] and others that dextrose and hepatic glycogen protect the liver against injury.

The prognosis in all cases is serious, recovery from severe involvement being rare. Weiss [10] stated that in the majority of cases death ensues by the end of the second week. Renal complications and hemorrhagic episodes increase the gravity of the outlook.

The following case is of interest because of the early age of the patient and because the diagnosis was not considered until necropsy.

REPORT OF CASE

A female infant whose birth had been entirely normal and uneventful was seen and examined by a pediatrician soon after birth and on several later occasions. The mother was 41 years of age, and this child was the result of her third

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7. Gay, T. B.: Atrophy of the Liver in Children, J. M. A. Georgia **22**:421-424 (Nov.) 1933.

8. Woolner, W.: Acute Yellow Atrophy of the Liver in a Boy Nineteen Months Old, Canad. M. A. J. **22**:283-284 (March) 1929.

9. Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, Arch. Int. Med. **23**:612-654 (May) 1919.

10. Weiss, S.: Acute Yellow Atrophy of the Liver, M. J. & Rec. **135**:316-321 (April 6) 1932.

pregnancy. Both previous pregnancies had been entirely uneventful and normal, and at the time of writing the children were living and well. The last pregnancy had been about eight years previously. The mother had been entirely well in the interim, and her menstrual periods always had been regular. During the early weeks of pregnancy she took some castor oil and quinine in an attempt to bring on the menstrual flow, but she denied taking any medication subsequently. Aside from mild nausea and vomiting during the first trimester the course of the pregnancy was entirely normal. The Wassermann and Kline reactions of the blood were negative just before delivery. Examination of a single specimen of urine gave negative results. The blood showed a hemoglobin content of 75 per cent (Dare); the erythrocytes numbered 4,270,000 and the leukocytes 9,900 in each cubic millimeter of blood. Labor began spontaneously and lasted about twenty-five hours. No sedatives were administered, and anesthesia was induced by inhalations of nitrogen monoxide with the pains for about sixty to seventy-five minutes before delivery, which was normal and spontaneous.

The infant was breast and bottle fed and got along well until the third day, when she refused breast and bottle feedings. On the morning of the fourth day bleeding from the umbilical stump and the vagina was noted. The coagulation time was eleven minutes, and the bleeding time exceeded thirty minutes. The infant was given 20 cc. of whole blood intramuscularly at noon. The coagulation and the bleeding time were each nine minutes that afternoon, and the intramuscular injection of whole blood was repeated that evening. Because bleeding from the umbilical stump, vagina, nose and mouth recurred periodically, intramuscular injections of whole blood were given twice daily on the fifth and sixth days and on the morning of the seventh day, in amounts of 30 cc. each time. Later on the seventh day bleeding became more profuse, and 100 cc. of whole blood was given intraperitoneally. Jaundice, which had been first noted about the fourth or fifth day as being slight, became severe. Purpuric spots appeared over all parts of the body, the infant's condition became progressively worse, and she died early on the eighth day after birth. No other laboratory studies were made.

The clinical diagnosis was probable hemorrhagic disease of the newborn.

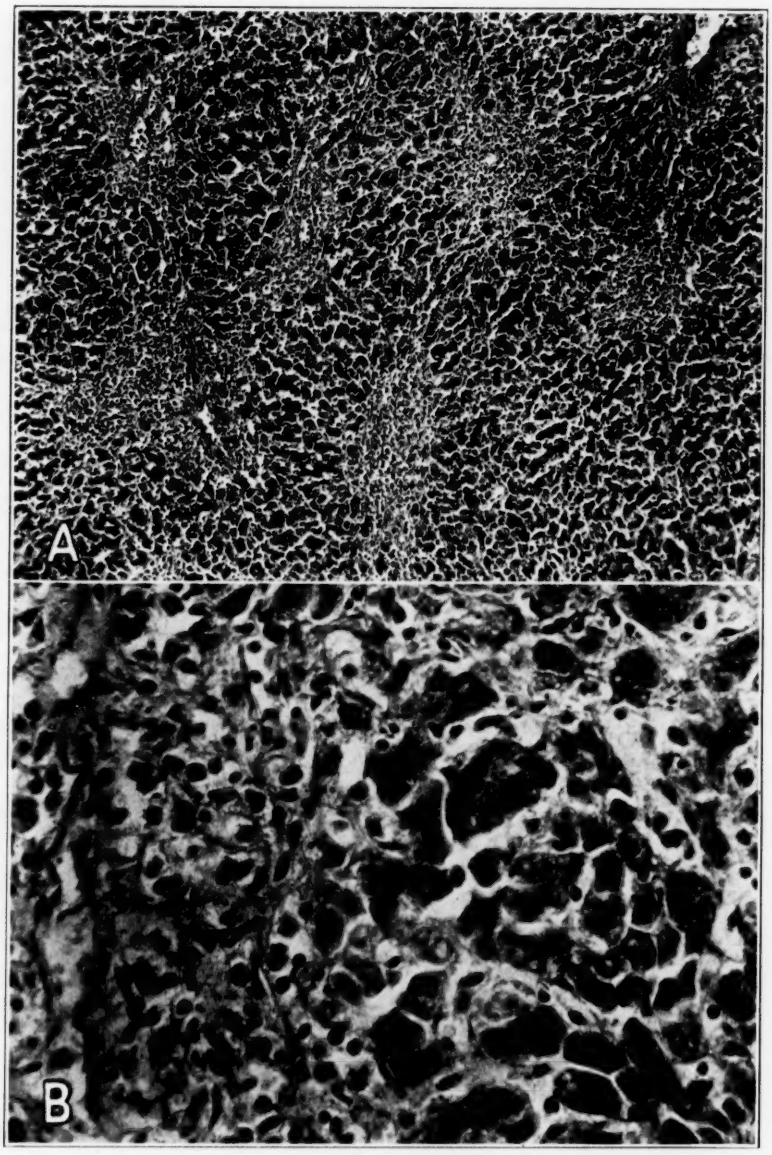
Necropsy.—The body was that of a fairly well nourished child with purpuric spots over the entire surface and evidence of bleeding from the nose, the mouth and the vagina. All the tissues and organs showed moderately severe bile staining.

The edge of the liver was above the costal margin, and the organ was approximately one-half the normal size, measuring 9 by 6 by 3 cm. and weighing 65 Gm. Its capsule was wrinkled and shriveled but not irregular, and the cut surface had a mottled greenish yellow color.

The gallbladder and the extrahepatic biliary passages appeared normal and were patent. The spleen was normal in appearance and size, weighing 6 Gm. Both kidneys were normal in size, with an icteric color and a few petechial hemorrhages. The uterus showed an area of hemorrhage in the posterior half of the mucosa. Both ovaries and tubes were entirely normal. The heart had few petechiae and was bile stained but otherwise normal. Grossly both lungs were entirely normal except for a pale icteric color. The gastrointestinal tract, the pancreas and both adrenal glands were bile stained but showed no evidence of hemorrhge. The brain showed gross hemorrhage over the cerebral and cerebellar hemispheres, but the source of hemorrhage was not apparent; otherwise the brain was grossly normal. There was no evidence of any gross trauma or infection.

Microscopically, sections of the liver showed extensive necrosis with some areas of degeneration at the periphery of some lobules as seen in the accompanying

illustration. The collapse of the stroma of the liver together with some leukocytic infiltration presented the appearance of increased fibrosis or fibrocellular replacement. The bile ducts were not conspicuous, and there was no evidence of regeneration. The destruction was uniformly distributed throughout the organ.



Sections of the liver of a newborn infant who died of acute degeneration of the liver. *A*, low power photomicrograph showing several areas of necrosis. *B*, high power photomicrograph showing the edge of one of the areas of necrosis.

Microscopic examination of sections of the other organs revealed nothing of significance.

COMMENT

The case presented here is of unusual interest because of the rarity of this condition at such an early age.

Despite painstaking investigation of the history, no suspected or probable etiologic agent could be uncovered.

Perhaps the question may be raised here as to the possible connection between this condition and some of the so-called hemorrhagic diseases of the newborn.

The clinical history of the case presented in this paper was supplied by Drs. Clarence E. Willcutt and Edward D. Anderson.

GINGIVAL TUMOR OF NEWBORN

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AND
THEODORE J. CURPHEY, M.D.
BROOKLYN

Massin [1] in 1894 reported a case of gingival tumor in which the growth occurred in a newborn child. He described the tumor as pedunculated and double. It was removed surgically, and the child made an uneventful recovery.

Füth [2] in 1902 reported a similar case. He was able to observe the child for two years after removal of the tumor. Instead of the first upper incisor a small gray stump grew at the previous site of the mass.

Gingival tumors of the newborn were discussed in a paper published by Pearson [3] in 1913. He reported a case of double tumor, one section being as large as an egg and the other the size of a strawberry. The growth occurred on the gingival edge of the maxilla, at the point of junction of the premaxilla and the main portion of the palate. The tumor was removed surgically, and the child made an uneventful recovery.

Kleine [4] in 1929 observed and reported 2 cases of pedunculated gingival tumor occurring in newborn female children. The pedicle in each case was attached to the region of the gum in which the second incisors later develop. Both tumors were removed and did not recur.

The most recent mention of this condition has come from South America, where Jorge and Nudelmann [5] observed 3 cases. The tumor in all 3 instances had a broad pedicle and was almost sessile. In 2 cases it occurred on the mandible and in 1 case on the maxilla. The teeth in 1 case were described as having erupted normally.

We wish to report a case recently observed by us, which is to the best of our knowledge the first case reported in America.

REPORT OF A CASE

History.—A white boy born in St. John's Hospital was transferred to the pediatric service of Dr. Paul Parrish, because of a new growth on the upper gum. The family history was essentially noncontributory. The mother's pregnancy

From the Pediatric Service, St. John's Hospital.

1. Massin, W. H.: Virchows Arch. f. path. Anat. **136**:328, 1894.
2. Füth: Verhandl. d. Gesellsch. f. Geburtsh. (1901), 1902, p. 74.
3. Pearson, W.: Tr. Roy. Acad. Med. Ireland **31**:405, 1913.
4. Kleine, H. O.: Arch. f. Gynäk. **138**:287, 1929.
5. Jorge, J. M., and Nudelmann, S. I.: Semana med. **1**:1933, 1932.

had come to full term, and delivery had been spontaneous, with vertex presentation. The boy was a first child whose birth weight was 8 pounds 5 ounces (3,741 Gm.). The respirations started spontaneously, and the cry was vigorous.

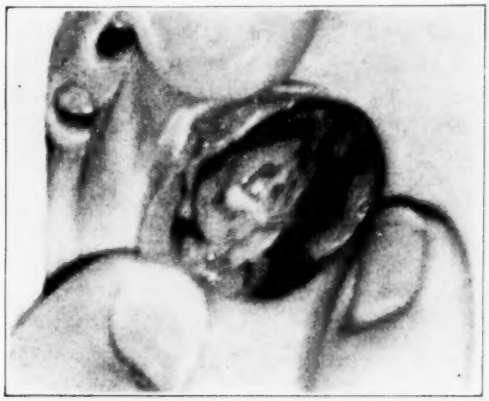

Fig. 1.—Multiple tumors growing from the ridge of the upper gum of a newborn infant.

Fig. 2.—Photomicrograph of a section of the tumor, showing large polyhedral cells with granular and vacuolated cytoplasm.

Physical Examination.—The child was well developed and well formed. The heart and lungs were normal. The spleen and liver were not palpable. Examination of the mouth revealed three distinct growths on the upper gingival ridge, at about the usual location of the right upper lateral incisor. The largest of the

masses was about 2 cm. in the anteroposterior diameter and 1.5 cm. wide. It had roughly the shape of an egg. This mass had a wide peduncle, and lateral to it and partly covered by it were two other growths, about the size of cherries. These were sessile. All three were covered by mucous membrane which was somewhat redder than the buccal mucous membrane. No other abnormalities were noted.

Laboratory Examination.—A blood count done soon after birth showed a hemoglobin content of 120 per cent and 23,000 white blood cells per cubic millimeter, of which 66 per cent were neutrophilic polymorphonuclears, 25 per cent lymphocytes and 10 per cent eosinophilic polymorphonuclears. The cholesterol content of the blood was 217 mg. per hundred cubic centimeters. Roentgenograms of the long bones were normal.

Treatment.—The masses were removed by electrocautery and the base cauterized by Dr. James Cobb. The gum healed readily, and the child was discharged.

Follow-Up Study.—The child was seen in the clinic three months later. There was a slight indentation at the previous site of the tumor. Roentgen examination of the teeth at this time showed normal preeruptive incisors.

Pathologic Report.—The tumor masses from the gum showed a normal squamous epithelial surface beneath which lay sheets of large polyhedral cells with small round nuclei lying in a bulky cytoplasm. The cytoplasm was granular and vacuolated and took the stain poorly, which gave the cells the typical "ground glass" appearance of lipoid histiocytes or xanthoma cells. It is worthy of note that there was absence of any limiting capsule between the cells and the overlying epithelium or the adjacent normal tissue. The diagnosis was lipoid histiocytosis.

COMMENT

The outstanding characteristic of gingival tumor is the location. It always occurs at the line of closure of the maxilla or the mandible. It may, therefore, be found on either side of the upper gum in the region of the second incisor on either side or in the midline of the mandible. It is benign, and simple removal effects a cure. It occurs in both sexes but more commonly in girls than in boys. A single tumor may occur, but often multiple growths are present. When the tumors are multiple one nodule usually is larger than the others. The larger tumors are pedunculated, and the smaller ones have a tendency to be sessile. The blood supply is usually rich. The tumors look and feel like small fibroids.

The greatest confusion exists as to the origin of gingival tumor. This is caused by the variable pathologic descriptions. Massin [1] stated the opinion that the condition is benign epithelioma and because of the location suggested that it arises from the cells of the enamel organ. This theory is given further strength by the report of Füth,[2] who observed a case in which microscopic section showed a perithelial structure. This case was observed for two years, at the end of which time there was a rudimentary peg instead of the first left upper incisor. This, according to Füth,[2] established the point of origin of the tumor as being the enamel organ. This fact has not been confirmed, and the question arises whether in removing the tumor the enamel body was not injured. Pearson [3] in

presenting a case observed by him concluded that the growth was a basicranial teratoma. McWeeney,[6] after studying the sections presented by Pearson,[3] stated that they were typical of lymphangiomyoma. Kleine[4] noticed that the cells of the tumors contained protoplasmic granules, and because of their staining qualities he concluded that they were mucoid. He advanced the opinion that such tumors histogenetically are derived from the basal epithelium. Jorge and Nudelmann[5] noticed similar masses and in the light of more recent pathologic knowledge concluded that they were xanthomatous deposits. The prevalence of lymphatic channels caused them to label the pathologic condition xanthomatous angiolymphangiomatous formations. In our own case the cells were reported to be xanthoma cells or lipoid histiocytes.

SUMMARY

A rare case of gingival tumor of the newborn is described.

Eight similar cases collected from the literature are summarized.

6. McWeeney, E. J., in discussion on Pearson.[3]

CHICKENPOX IN A TWELVE DAY OLD INFANT

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Chickenpox in the very young infant has been described by several authors,[1] but the disease rarely occurs earlier than the beginning of the second week. Even though knowledge about virus diseases has increased rapidly during the past decade, there are still prominent and important features that need investigation. Often the study of a rare, unusual or extreme condition leads to important information concerning the biologic aspects of a disease. An example of this is Jenner's interest in the milkmaid's immunity to smallpox, which led him to the appreciation of an important immunologic principle. The following case is reported because it is unusual and because it provides data concerning the treatment of varicella in early infancy.

REPORT OF A CASE

L. N., a 20 year old housewife, was admitted to Walter Reed Hospital on Feb. 5, 1938, for the delivery of her second child. She had been observed monthly at the obstetric clinic during this pregnancy. Her past history and family history were not important, except that she said she had not had chickenpox or herpes zoster. Seventeen days prior to the birth of this child, she was exposed to chickenpox. One day after the birth of the child and eighteen days after exposure, the mother was noted to have a fever and a sparse vesicular rash on her face, chest and abdomen. She had a mild attack of varicella and recovered without complication.

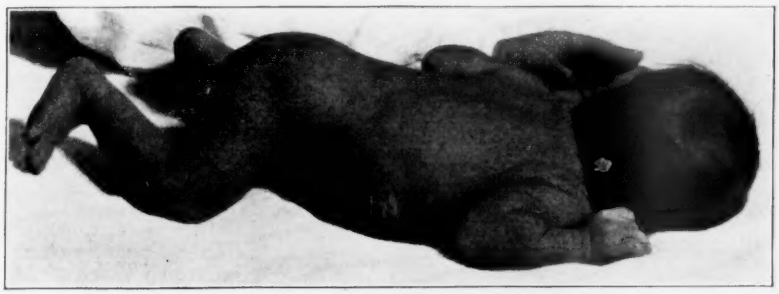
The infant was born on February 6, weighing 7½ pounds (3,189 Gm.); delivery was spontaneous, with no complications. The child was allowed to feed from the mother's breasts, as it was thought that her milk might contain immune bodies. On the eleventh day after birth the child was irritable and had gained only ½ ounce (14 Gm.) in weight instead of the 2 or 3 ounces (57 to 85 Gm.) it had been gaining during the previous days. On the twelfth day a generalized erythematous and vesicular rash appeared. Shortly after the appearance of the rash 10 cc. of the mother's blood was injected into the child's buttocks. There were several successive crops of vesicles during a seven day period, and finally the disease subsided. The child recovered without complication or sequelae.

From the Infectious and Contagious Section of Walter Reed General Hospital.

1. (*a*) Pridham, F. C.: Chickenpox During Intrauterine Life, Brit. M. J. **1**:1054 (May 17) 1913. (*b*) Baron, F.: Un cas de varicelle mortelle chez le nouveau-né par contagion maternelle, Nourrisson **23**:157 (May) 1935. (*c*) Lereboullet, P.: Clinique médicale des enfants, Rev. gén. de clin. et de thérap. **51**:97 (Feb. 13) 1937. (*d*) Henderson, W. B.: Chickenpox in an Eight-Day-Old Infant, J. Pediat. **4**:668 (May) 1934.

COMMENT

The course of events in this case fixes the mother's incubation period at eighteen days. If the incubation period of the child's attack is calculated from the stage of eruption of the mother, it is eleven days. If it is calculated from the time of the delivery, it is twelve days. The time between the exposure of the mother and the eruption of the infant is twenty-nine days. Since the mother had no eruption at the time of the delivery, it is reasonable to assume, according to the current belief expressed by Goodpasture,[2] that the virus in this case was still localized in the epithelial tissues of the mother's nasopharynx and that the general invasion of her body had not occurred. The cases of Henderson [1d] and Baron [1b] show that the virus may invade the fetus just before birth. In the case here reported the period of twenty-nine days was too long to have been an incubation period for the infant, and it is felt that the



A 14 day old infant with chickenpox.

child was exposed and the virus gained entrance at the time of birth. A consideration of the incubation periods in the cases just mentioned lends support to the idea that the fetus was invaded by the virus just before the appearance of the rash in the mother. One cannot be dogmatic about the way this virus is transmitted without taking into consideration the cases reported by Hubbard [3] and Pridham.[1a] Each of these authors reported a case in which the rash appeared on an infant at birth. In each case the mother did not have chickenpox but the disease had been present in other members of the family during the two weeks prior to the birth of the infant. These cases suggest the possibility that the virus gains entrance into the fetus by passing through the immune mother. Concerning smallpox, Shamberg and Kolmer [4] stated: "It is an

2. Goodpasture, E. W.: Comments on Virus Diseases and Their Control, South. M. J. **30**:731 (July) 1937.

3. Hubbard, T. W.: Varicella Twenty-Four Hours Post-Partum, Brit. M. J. **1**:822, 1878.

4. Shamberg, J. F., and Kolmer, J. A.: Acute Infectious Diseases, Philadelphia, Lea & Febiger, 1928, p. 159.

acknowledged fact that a woman, though personally immune, may give birth to a child suffering from smallpox; it is probable that in such cases the mother has passed through a variola sine exanthema." By analogy the same situation might obtain with varicella.

Chickenpox in early infancy is a serious complication. The mother and infant should be isolated as soon as the diagnosis is made. Whether the infant should feed from the mother's breasts or not depends on the severity of the disease in either the mother or the infant. Agglutinins for the varicella virus have been demonstrated in the blood as early as the fifth day after the onset of the eruption.[5] I do not know whether they have been demonstrated in the milk of mothers who were recovering from chickenpox. The use of convalescent serum and/or injection of whole blood are recognized methods of treatment, and a review of this case suggests that they might be more effective if employed before the stage of eruption.

SUMMARY

A case of chickenpox in an infant 12 days old is reported in which the date of exposure and the date of eruption of the mother and the date of eruption of the infant are accurately known.

Treatment consisted of isolation, intramuscular administration of whole blood and general supportive measures.

Lt. Col. Joseph F. Gallagher and Dr. John H. Voegtly gave help and suggestions in the treatment of this patient.

5. Amies, C. R.: The Elementary Bodies of Varicella, Lancet **1**:1015 (May 13) 1933.

Progress in Pediatrics

DEVELOPMENT OF PEDIATRICS AND OF PEDIATRIC TRAINING IN SWEDEN

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Earlier than in any other country, that is, in 1845, pediatrics was recognized in Sweden as a medical and scientific specialty, when the government required compulsory instruction in pediatrics for all students of medicine. In the same year, earlier than in any other medical school in the world, a full professorial chair in pediatrics was founded at K. Karolinska Mediko-Kirurgiska Institutet. This medical college, organized by the national government in Stockholm in 1810 in competition with the old universities at Uppsala and Lund, developed gradually into the outstanding medical school in Sweden. The first incumbent of this chair was the esteemed Dr. Fredrik Theodor Berg, a physician distinguished for his scientific and clinical work and well known because of his discovery of the cause of sprue. The large state orphanage in Stockholm, Allmänna Barnhuset, to which Dr. Berg had been appointed as directing physician in 1842, was designated as the place of instruction for the new specialty. This orphanage carried on its function as a clinical-pediatric teaching institution from 1842 until 1932, when it was decided to move the pediatric clinic and to bring it into closer relation with Karolinska Sjukhuset (Caroline Hospital), which is being built by the state for the purpose of medical teaching. This hospital is expected to comprise all of the clinics of Karolinska Institutet, and at a time not too far in the future all of the theoretic divisions of the institute will be moved to the same location.

In 1851 the orphange was enlarged by an outpatient clinic for sick children, which also was placed at the disposal of medical education and which, moreover, acquired great importance as a child welfare center, where mothers could obtain advice about the care of children.

The large orphanage in Stockholm, which has been closely connected with training in pediatrics and even more closely with social provision for children, owes its beginning to the greatly advanced ideas of social reform held by King Gustavus Adolphus II, the greatest of the kings of Sweden. In the year 1624 he issued an edict with provisions which were remarkably modern in tone. The decree ordered that all subjects

who were willing and able to work should be given work; that all who, though willing, were incapacitated for work by illness or physical handicaps should be taken into hospitals; that indigent persons who were able but unwilling to work should be sent to prison, and that destitute children should not be admitted into hospitals but should be provided for in separate children's homes built for that purpose. All begging was forbidden. The constant wars and the high cost of building the various institutions mentioned hindered the completion of such extensive plans at the time, but some of them were carried out. The outstanding accomplishment was the erection of the Orphanotrophium (Allmänna Barnhuset) in Stockholm. By means of lands granted by the state in 1633, 1637 and 1650, through privileges and shares in certain forms of taxation, through outright gifts of money from the government and from private persons and later through additional public support, this asylum continued to function until the middle of 1932, when it was completely reorganized. After that time its resources were used partly for the provision of a selected number of private children's homes, to which local authorities could confidently assign needy children, and partly for the support of homes for mothers and infants, as well as for temporary asylums for older children. However, 1,000,000 kronor was given toward the building of the new children's clinic in Karolinska Sjukhuset.

The legal status of the Orphanotrophium was somewhat peculiar. Although the institution was founded and maintained by the state, it was given the stamp of a charitable organization and was placed under the direction of a board of trustees, whose members were chosen by the government at various times from the ranks of high officials of the national government and of officials of the city of Stockholm. In this selection the government never took into account whether or not the appointees possessed any special experience or interest in the social care of children, and so the trustees cannot always be cleared of the charge of selfish gain, or at least of negligence, in the management of financial affairs. The charitable effectiveness and the financial condition of this richly endowed institution were therefore as a general rule unsatisfactory. In 1733 an investigating commission appointed by the parliament described the situation as follows: "For all the tons of gold which have been provided for the children's home since its founding, the nation has received little evidence that there has developed a single moderately useful human being." And during succeeding years a similar conclusion would have been justified. Perhaps in our own day experts would be less prone to condemn such failure than the judges of earlier years. Now we know what was not known in these times: namely, that in social medicine, as in the whole art of healing, prophylactic measures play the leading role.

In modern terms, the Orphanotrophium in Stockholm, as well as several smaller homes for children built in provincial cities, consisted of a combination of children's home, charitable boarding school and reform school; only children over 6 years of age were admitted, and they remained in the institution until they could be apprenticed to tradesmen or until they were capable of carrying on manual labor, housework or a similar occupation. The number of charges in the asylum from the time of its origin until 1763 never exceeded 200; for many years there were only half or a third of that number, or even less. After the period from 1763 to 1766, when a thorough reform was instituted, this number rose to 300 or 400.

The continued fruitlessness of the work of the asylum led in 1785 to reorganization on entirely new principles. Instead of being an educational institution for older children the orphanage became a temporary asylum for children who were later assigned to private children's homes scattered all over the country, where they received care and schooling in return for remuneration paid by the institution. From this time those admitted were generally infants, older children being received in much smaller numbers than formerly. Children who became ill in the asylum remained there as long as their illness necessitated, and those who fell ill in the private homes were brought back to the hospital division of the asylum for the necessary care. After reorganization the average daily number of sick infants who were cared for within the walls of the asylum was 14 for a number of years, and the average period of illness was twenty-eight days; later the figures rose to 56 children and fifty days of illness. During the latter half of the nineteenth century the average annual number of infants ranged from between 75 and 80 to between 100 and 200 and the days of nursing from between fifty and sixty-five to between seventy and one hundred and fifteen. During the first two decades of the present century the average daily number of hospitalized infants varied for different years from 190 to 230 and the average number of days of sick care from eighty-five to one hundred and twenty. The average number of all children (infants and older children) hospitalized in the buildings of the institution during these two decades varied between 269 and 310.

The average number of all children placed under the care of the institution (within its walls and in private homes) remained between 2,000 and 3,000 during the first half of the nineteenth century. Toward the end of that century the figure increased to over 4,000. The maximum was reached in the second decade of the present century, when the figure was about 6,000. Owing to the newly introduced laws for the protection of children (which forbade the anonymity of parents, vehemently

attacked the desertion of children and specifically fixed the responsibility of both parents of an illegitimate child for its support), the number of children admitted to the asylum sank drastically, simultaneously with the total number of its charges. In about a year the figure dropped to approximately 1,000, and in 1932 it was about 300. In the latter year, as already mentioned, the previous functions of the institution were discontinued, and the earlier type of clientele soon vanished completely. The influence of the new laws in decreasing the number of state charges can easily be understood. For one thing, the majority of the charges admitted into the asylum since 1785 have no longer been accepted free of charge but have been taken in return either for nursing service given by unmarried mothers or for a certain sum of money in cash or have been accepted because of desertion by the parents. Another factor is that children have left the protection of the institution at the age of 14, to become members of the families with whom they had been placed.

During the many years between 1785 and 1932 there has naturally been a great variation in the mortality of the total group of children. Only a few figures on the mortality of infants will be given here. Total figures for infants (both in the asylum and in private homes) are not known up to the middle of the nineteenth century. During the five decades between 1850 and 1899 the total annual mortality varied from 20 to 30 per cent, 13 to 23 per cent, 10 to 31 per cent, 8 to 29 per cent and 14 to 33 per cent, respectively. During the first two decades of the present century the corresponding averages varied from 12 to 23 and from 6 to 14 per cent.

The mortality of infants hospitalized within the asylum in the twenty-five years immediately after the reorganization of 1785 probably averaged 50 per cent or more, and in the next twenty-five years the average was 34 per cent.

In regard to these figures for infant mortality within the asylum it must be remembered that since 1788 the infants have been fed on breast milk by wetnurses, who were occasionally the infants' mothers. In the years from 1788 to 1814 a nurse fed on an average from 1½ to 2 children and from 1815 to 1841 an average of 1½ children. The last figure can also serve as the average for the remaining years of the nineteenth century. In the years 1900 to 1932 the relative number of nurses decreased, a single nurse feeding an average of 2½ children. That the mortality was so high until recent years in spite of the abundant supply of breast milk will not be astonishing to any one who is familiar with the history of children's and foundlings' homes of bygone centuries. In any case the asylum at Stockholm had an unusually low mortality as compared with that of all similar institutions of the past. Even when the asylum was in a precarious state, for reasons previously indicated,

the results of the nourishment and care provided within the main home were favorable, and the mortality was as low as that of royal families. But the picture even now was shadowed by the high mortality among infants placed with foster parents. This raised the total mortality for all infant charges of the institution and for the entire group of children above the corresponding mortality of all illegitimate infants and children in the entire country. The great annual expenditures (in this century about 1,000,000 kronor) therefore had yielded nothing.

The drop in mortality, the corresponding decline in morbidity and the gradual exhaustion of the clientele within the home made the asylum unsuited for instruction in pediatrics. However, clinical material was supplied—not without the opposition of the board of trustees—by the intervention of the government. From 1919 on some of the rooms were devoted to the quartering of sick infants and older children. This hospital division, now comprising 75 beds, is to remain in the asylum buildings until the new children's clinic of Karolinska Sjukhuset is completed.

With the dates mentioned I have outlined the history of the first clinic for pediatric instruction in Sweden, which has functioned continuously up to the present. The first (ordinarius) professor of pediatrics introduced into this clinic a course in pediatrics remarkably good for his time. Its main characteristics were rigid limitation of the number of students (the maximum still is 25) and extensive participation of students in all clinical work and routine in the clinic, the outpatient clinic and the laboratory.

After the resignation of Berg from his position as professor of pediatrics in 1854 (he accepted a post as chief of the national health office), H. A. Abelin was appointed professor of pediatrics at Karolinska Institutet, remaining from 1855 to 1882; then followed A. Kjellberg (1882 to 1884), K. O. Medin (1884 to 1912), I. Jundell (1912 to 1932) and W. Wernstedt (1932 to 1937).

As early as 1861 a second teaching chair in pediatrics was founded at Karolinska Institutet. The first occupant of this chair was an assistant to the professor ordinarius, but in 1879 he became first a lecturer and then a full professor in pediatrics, with the same teaching duties as the first professor. Thus Karolinska Institutet became the first and was until recently the only medical college which had two full chairs in pediatrics. The incumbents of this second position were A. Kjellberg, first as assistant (1861 to 1879) and then as professor (1879 to 1882), K. O. Medin (1883 to 1884), J. Waern (1885 to 1914), W. Wernstedt (1921 to 1932) and A. Lichtenstein (1932 to the present time).

The classes of the second professor of pediatrics were moved in 1885 to the Kronprinsessan Lovisas Vårdanstalt för Sjuka Barn, a hospital erected and maintained by private means.

Up to 1915 all Swedish medical students had to take the required course in pediatrics at Karolinska Institutet in Stockholm. If they desired they could receive in the general clinics and in the children's clinics of the universities in Lund and Uppsala instruction by the local professors of pediatrics, who themselves determined its standard and extent. Not until 1900 and 1915, respectively, did the universities at Lund and Uppsala establish clinics for sick children. At about the same time these clinics and their directors were brought up to the standard of the clinics of Karolinska Institutet in regard to type of instruction and teaching duties. The following summary will shed further light on instruction in pediatrics as given by Swedish universities.

At the University of Lund in 1879 a university lectureship in pediatrics was established. In 1889 it was changed into a lectureship and in 1909 into a professorship in pediatrics and practical medicine. In 1935 this position was converted into a chair limited to pediatrics. The incumbents of these respective chairs were F. Lennmalm (1889 to 1890), C. H. Hildebrand (1891 to 1916), K. D.af Klercker (1916 to 1933) and S. Siwe (1936 to the present time). Before 1900 there was in Lund only an outpatient clinic for children; in 1900 a children's clinic was also established.

At the University of Uppsala in 1877 (not until 1884 de facto) a university lectureship in pediatrics and practical medicine was established. In 1915 this chair was converted into a position limited to pediatrics alone. Incumbents of these positions were O. V. Petterson (1884 to 1909), Gunnar Forssner (1911 to 1912), R. Friberger (1912 to 1915), G. Bergmark (1915 to 1923) and A. I. Thorling (1923 to the present time). From 1884 to 1915 only an outpatient clinic was available; then a children's clinic was also added.

At present the average medical course of study in Sweden up to the passing of national board examinations takes nine years. For official recognition that a physician is qualified as a practicing specialist the Swedish Medical Society (a private general medical association to which nearly all physicians and assistant physicians in private practice belong) requires at least three additional years of training in the special field, a part of which is spent in clinics. This holds good for pediatricians. At the close of 1937 there were a total of 3,238 physicians in Sweden (practicing and not practicing). At the same time there were 83 physicians who had earned the permission of the medical society to be listed as specialists in children's diseases.

OBSERVATION OF GROWTH OF CHILDREN IN PEDIATRIC PRACTICE

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The guidance of the care and training of young children has become an important service rendered by pediatricians. This service is concerned with the recognition and treatment of defects or disease, with the prevention of infectious diseases, with adequate provision for nutritional and other needs and with the establishment of routines, habits and attitudes consistent with health. It requires the study of developmental characteristics and the observation of growth, as well as the search for and recognition of pathologic conditions. The former requires broad knowledge and deals with diverse fields of science.

The care which is best suited to meet the needs of a child depends not only on his age but on the stage of development through which he is passing at the moment and on his individual characteristics. First, therefore, the program for the care of any child at any age should be worked out on the basis of the features of the human pattern at this age and their significance in respect to health needs. Second, the program should be planned with full appreciation of the child's individual developmental attributes. It should be kept abreast of the child's changing needs. Repeated assessments are essential to an understanding of the course which the development of any person is taking and of his changing needs. Effective health service requires especially the ability to take a long time view of the significance of the present findings, and this can be attained only through continuing experience with the same child. Rigid application of generally acceptable routines without medical study has both limitations and dangers.

In this paper attention will be confined to the recognition and interpretation of the manifestations of growth. The knowledge of human growth and development has been referred to as the basic knowledge specific for and fundamental to pediatrics; it is certainly essential for intelligent guidance of child care. The pediatrician should be thoroughly conversant with the knowledge relating to human growth, as to both

Summary of address given before the Chicago Pediatric Society, Nov. 12, 1938. This subject was chosen because of the meeting of the Society for Research in Child Development in Chicago at this time and because the writer was chairman elect of that society.

general trends and the extent of individual differences. He should appreciate what phases of growth tend to be orderly and regular and what phases are commonly irregular. He should have some notion of the unusual features, which tend to occur together, and of the inadequacies with which they are commonly associated. He must also appreciate the influence of these differences on individual needs.

The conventional medical approach, depending on early training and ignorance as to the fundamental science of growth, has tended to block the development of a natural interest in these problems on the part of many physicians. Following the course of events in the countless different individual patterns which children present can become a fascinating undertaking.

DEVELOPMENTAL EXAMINATION

The information required for proper understanding of a child's needs calls for a developmental and health history and for a developmental as well as an ordinary medical examination. These are satisfactory only when built up through periodic reexaminations. The features with which one is concerned in assessing individual differences are diverse. They include size and proportions (proportionate development of soft tissues as well as skeleton), general and specific rates of growth, stage of maturation of the various parts or systems, qualities of the various tissues, physical capacities or fitness, experiences, reactions and habits, nervous and emotional stability and special weaknesses or susceptibilities as well as assets.

There are certain questions which the pediatrician should form the habit of asking himself after performing a developmental examination:

What sort of individual is this child, and how does he compare with other children?
How unusual are his special attributes?
What bearing do the individual features observed have on his fitness and needs?
What bearing may they have on his future health and development?
In what ways and to what extent is he changing with growth?
Is his progress symmetric and consistent, or is it disorderly?
How has his recent rate of progress compared with expectancy?
How are these changes affecting his needs?
Having decided that certain features are undesirable, the physician inquires:
Are these features inherent or the result of faulty care and environment?
How are they likely to change in the normal course of development?
In what way do they call for modification in care?
In what way can they be corrected or compensated for?

Data relating to many attributes should be obtained by various means and as far as possible should be evaluated in respect to chosen standards.

It is more commonly impossible to be precise than otherwise in answering these questions, but a recognition of general trends may be useful. For example, there is no exact measure of the mass of a child's muscles, and there are no standards as to what should be expected in their development. It is possible, however, by observing their functions, by feeling size and firmness, by observing their mass in roentgenograms and by measuring certain circumferences to recognize muscles which are relatively underdeveloped.

USE OF MEASUREMENTS

The taking of a few measurements routinely at periodic examinations has been found helpful in securing and holding parental interest in making these examinations regular. They occasionally give early evidence of the presence of disease. Measurements are of value primarily in portraying the characteristics of individual growth. In considering measurements, the chief difficulty at the moment is the absence of suitable standards with which to compare the growth of an individual. It is possible, however, to detect disorderly growth or asymmetry in growth. Research has been too largely devoted to the development of indexes of growth, which are not necessary for the recognition of unusual growth and which are often confusing. An attempt is now being made to assemble suitable standards which the physician can use to determine to what extent a child is unusual. Measurements should be thought of as portraying growth trends. Their significance in respect to nutrition, functional adequacy and the like should be decided not arbitrarily but only after careful consideration of all pertinent historical data and of other features of the examination. There are many measurements which can be taken with reasonable reliability, but for purposes of recognizing the general characteristics of growth during the early years, length of the body, circumference of the head and chest and pelvic breadth seem adequate. They may be evaluated to best advantage by study of the curves which they plot at successive examinations in respect to appropriate norms. The curves for the different measurements may be compared directly.

Following the growth of children as they approach and pass through the adolescent period is of special interest. Growth at this period has been considered disorderly and irregular, but this has been due to the study of growth trends in relation to chronologic age. When stage of maturation is considered, growth at this period is found to be surprisingly orderly.[1]

1. Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monograph of the Society for Research in Child Development, National Research Council, 1937, vol. 2, no. 5 (serial no. 12).

FEATURES OF DEVELOPMENT NOT SHOWN BY MEASUREMENT

The developmental examination includes observations of many features not revealed by direct measurements. In respect to many of these the observer is concerned only to know how usual or unusual the person under examination may be. It is often possible to place a child in an appropriate rank for a particular attribute with respect to children of his age and sex, even though this attribute cannot be measured exactly. In interpreting the significance of any particular position within the normal distribution, however, it is important to be aware of the wide differences between the ranges of these distributions at different ages and with different attributes. For example, the capitate and the hamate bone become opaque to roentgen rays with great uniformity in normal boys during the first six months of life. The presence of these centers at birth or their absence at the age of 6 months is sufficiently rare to justify a search for other evidences of unusual development. The triquetral and the lunate bone, however, appear at any age between 6 months and 5 years with almost equal frequency, so that attention to their presence or absence in early childhood is not justified. The range of values obtained for any one attribute also varies with age. For example, the distribution of hemoglobin values obtained from studies of apparently normal infants at the age of 1 year is wide, whereas among 4 year old children little variation is encountered.[2]

PRINCIPLES TO BE OBSERVED IN FOLLOWING GROWTH

There is a human pattern of growth.

There are extensive individual variations within this pattern, but these tend to be orderly.

Some children are far more orderly in growth than others. Some developmental items show less individual variation than others and are therefore more significant.

Health problems tend to arise more commonly among the extreme deviates than among the more regular in pattern.

The magnitude of increments is apparently not as important as symmetry, proportion and balance in growth.

The time of occurrence is not as significant as the order or sequence of occurrences. Chronologic age is by no means a perfect gage of development.

The natural forces within the child are working toward the ultimate elimination of excessive deviations. Thus the small child grows over a longer period than the larger one. Acceleration beyond the normal rate apparently follows periods of excessive retardation.

Dietary inadequacy, fatigue and lack of use or activity are the principal environmental forces known to interfere with normal progress. Illness may or may

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2. Guest, G. M.; Brown, E. W., and Wing, M.: Erythrocytes and Hemoglobin of Blood in Infancy and in Childhood: Variability in Number, Size and Hemoglobin Content of Erythrocytes During the First Five Years of Life, Am. J. Dis. Child. **56**:529 (Sept.) 1938.

not interfere with growth. Its influence may be direct but more commonly appears to operate through one or another of these factors.

The physician's opportunities to promote growth are limited, but he is often able to remove retarding factors, to protect during temporary periods of inadequacy and to aid the family and child in adjusting to or compensating for limitations.

NEED FOR RESEARCH IN CHILD DEVELOPMENT

Practical application of these principles is largely thwarted by lack of knowledge relating to child development. Pediatricians interested in research have been so preoccupied with the study of disease that they have not contributed as much as might have been anticipated to studies of normal development. There is much attainable information which is urgently needed for effective child care but which is not available at the moment. Much information respecting normal child development has been acquired by members of other disciplines and is not readily accessible to pediatricians. These workers have been concerned in the main with determining how children grow. Some attention has been devoted to the significance of different patterns of growth, particularly with respect to nutritional needs and educational problems. The pediatrician could contribute particularly to a better understanding of the conditions which modify growth unfavorably. He is in the best position to determine how interference with growth can be avoided and more satisfactory growth can be promoted through health measures and medical procedures. It is surprising how little is really known about the effects of disease on growth, in view of the attention given to sick children.

SOCIETY FOR RESEARCH IN CHILD DEVELOPMENT

This society was founded four or five years ago to provide a professional association in which the many different groups concerned with the study of children can interchange views concerning subjects not restricted to one field. It serves to bring to the attention of one group valuable contributions of another. The best interests of pediatrics would undoubtedly be served if the prejudices and barriers, built on ignorance and misunderstanding, between pediatricians, physiologists, psychologists, sociologists and nutritionists could be broken down. This is essential for the successful prosecution of research in child development. It is one of the principal objectives of the society. The biennial meetings of this society offer pediatricians an opportunity to become acquainted with the leading investigators from the allied disciplines and to learn of research findings often hidden in the publications of these groups. The publications of the society also afford an opportunity to keep in touch with the broader literature on child development.

News and Comment

GENERAL

American Board of Pediatrics.—The American Board of Pediatrics will hold examinations on November 14 and 15, in Cincinnati, preceding the annual meeting of the American Academy of Pediatrics. Appointments for this examination must be made before July 14, 1939.

Directors of Italian Pediatric Clinics Appointed.—By a recent governmental decree the following professors were appointed directors of pediatric clinics: Gaetano Salvioli at Bologna, Giancarlo Bentivoglio at Pavia, Michele Gerbasi at Siena and Cesare Cocchi at Parma.

Sixth Pacific Science Congress.—The Sixth Pacific Science Congress of the Pacific Science Association will be held in San Francisco, Berkeley and Stanford, Calif., from July 24 to Aug. 12, 1939.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

DIFFERENTIATION OF PATHOGENIC STAPHYLOCOCCI FROM NON-PATHOGENIC TYPES. G. H. CHAPMAN, C. BERENS, E. L. NILSON and L. G. CURCIO, J. Bact. **35**:311 (March) 1938.

Degeneration of staphylococci produces mixtures of dissociants with different pathogenic properties. Therefore, it is important to separate variants before applying tests for pathogenicity. Certain details of technic must be observed in order to obtain the best results. An effort has been made to arrive at possible sources of error by analysis. With appropriate technic and by interpreting results as suggested in this paper, it is possible to obtain a correlation between the results of certain in vitro tests, the results of rabbit inoculation and results based on the source of the culture. The coagulase test is the most reliable single test for the differentiation of pathogenic from nonpathogenic staphylococci. Hemolysis of rabbit blood agar when used in conjunction with the pigment and the coagulase test permits simple estimation of the degree of pathogenicity of a strain or variant. Tests with methylrosaniline agar and bromthymol blue agar and for mannitol fermentation are useful as supplementary tests. The two latter are more useful for isolation than for differentiation.

STOESSER, Minneapolis.

ANTIBACTERIAL ACTION IN VITRO OF 2-(P-AMINOBENZENESULPHONAMIDO) PYRIDINE ON PNEUMOCOCCI AND STREPTOCOCCI. A. FLEMING, Lancet **2**:74 (July 9) 1938.

Sulfapyridine (2-[para-aminobenzenesulfonamido] pyridine) in concentrations which it is reasonable to suppose can be obtained therapeutically was found to retard the growth in human blood of pneumococci and hemolytic streptococci. Blood containing it in such concentrations can destroy considerable numbers of pneumococci and streptococci. Leukocytes are necessary for such destruction. If the blood is rendered "immune" by the addition of some specific immune serum the apparent effect of the chemical is enhanced. It is suggested that to obtain the best results with the drug patients should be immunized actively or passively.

Similar experiments were performed with sulfanilamide, and it was found that the pyridine derivative has a greater antipneumococcic and antistreptococcic action than has sulfanilamide.

LANGMANN, New York.

Metabolism; Infant Feeding; Milk and Other Foods

CREATINE-CREATININE METABOLISM AND THE HORMONES. P. PIZZOLATO and H. H. BEARD, Endocrinology **24**:358 (March) 1939.

Various "hormone" preparations were injected into normal and castrated rats, and the effect on creatine-creatinine metabolism was studied. The result was an increase in excretion of creatine accompanied by a decrease in excretion of creatinine. This inverse relationship between creatine and creatinine excretion offers proof that creatinine is transformed into creatine in the body and that it stimulates the excretion of both creatine and creatinine in the urine. The transformation of creatine into creatinine does not occur in the rat or in man. A possible synergistic action of the hormones in the body on creatine-creatinine metabolism is suggested.

JACOBSEN, Buffalo.

DRUGS TRANSMITTED THROUGH BREAST MILK: II. BARBITURATES. R. M. TYSON, E. A. SHRADER and H. H. PERLMAN, J. Pediat. **13**:86 (July) 1938.

Phenobarbital U. S. P. and soluble phenobarbital U. S. P. were administered to lactating mothers in sedative and hypnotic dosage. For sedative effect ½ grain (0.03 Gm.) was given four times daily, and for hypnotic effect 1½ grains (0.09 Gm.) was administered at bed time. Analyses of individual specimens of milk from mothers to whom the drug was administered in small doses at regular intervals did not show as high a percentage of the drug in the milk as did specimens obtained from mothers each receiving a single larger dose. Concentrated dosage seemed to have more effect in the transmission of the drug to the milk than cumulative dosage. In only 2 of 41 cases was there clinical evidence of effect on the nursing infant.

RAUH, Cincinnati.

DRUGS TRANSMITTED THROUGH BREAST MILK: III. BROMIDES. R. M. TYSON, E. A. SHRADER and H. H. PERLMAN, J. Pediat. **13**:91 (July) 1938.

Ten lactating mothers were given 1 Gm. of sodium bromide every four hours, beginning on the sixth day post partum and continuing until discharge from the hospital. Analyses of the breast milk showed the presence of the bromide in 97.37 per cent of the samples of milk examined. Clinical evidence of transmission of the drug was manifested to a marked extent in 4 cases, and in all 10 cases there was marked diminution in irritability in the child as well as in the mother.

RAUH, Cincinnati.

EFFECT OF CALCIUM LACTATE ON CHILDREN IN A NURSERY SCHOOL. W. R. AYKOYD and B. G. KRISHNAN, Lancet **2**:153 (July 16) 1938.

This report is from the Nutrition Research Laboratories of the Indian Research Fund Association, Conoor, South India. The average age of the children studied was 4½ years. They belonged to middle class and lower middle class families, and it was assumed that their diet consisted largely of milled rice and that their intake of milk and vegetables was low.

They were given 0.5 Gm. of calcium lactate daily and showed greater increases in height and weight during a four to five month period than children not receiving the supplement.

Supplements of calcium salts are recommended as a substitute for milk when milk cannot be supplied.

LANGMANN, New York.

TREATMENT OF MARASMUS BY INJECTION OF AN EXTRACT OF ADRENAL CORTEX. W. A. HISLOP, Lancet **2**:308 (Aug. 6) 1938.

Sometimes, even when the primary cause of marasmus has been removed and both quantitative and qualitative errors of diet corrected, an infant with this condition fails to improve, either from inability to take enough food or from inability to absorb or utilize it.

It seems probable that inanition in infants from any cause will lead after a time to secondary hypofunction of the adrenal glands, with or without gross structural changes.

The results of a study of two series of 5 and 14 infants, respectively, who were being given an extract of adrenal cortex suggested that adrenal hypofunction was corrected in part at least by the drug. The infants gained more during the periods when the drug was being given than when it was not given.

LANGMANN, New York.

NUTRITION OF CHILDREN. E. H. M. STEPHEN, M. J. Australia **2**:228 (Aug. 13) 1938.

Stephen presents a review of the essentials of diet for children, together with a plea for considerable latitude of choice.

TENNEY, Madison, Wis.

NUTRITION OF THE CHILD. F. S. HANSMAN, M. J. Australia **2**:233 (Aug. 13) 1938.

This article is a plea for simplicity in feeding. The author states that the science of nutrition is "as complex as life itself" but that the practice of nutrition is simple and is summed up by saying, "Eat what nature provides."

TENNEY, Madison, Wis.

VARIATIONS OF THE KETONE BODIES IN RELATION TO LIPOGLYCOCHOLESTEREMIA IN NORMAL AND PATHOLOGIC CONDITIONS IN CHILDHOOD. E. MEDDA, Arch. ital. di pediat. **6**:1 (Feb.) 1938.

Medda reviews the literature on the chemical content of the blood in the presence of various pathologic conditions. The review is accompanied with an extensive bibliography. For 32 normal children of various ages he tabulates determinations of the acetone, acetoacetic acid and total ketone bodies in the blood; for 50 children with measles, diphtheria, pneumonia, varicella, pertussis and typhoid and for 44 children with a wide variety of noninfectious conditions, including diabetes, nephritis, digestive disturbances, dyscrasias of the blood, tumors of the brain and various endocrine disturbances, he tabulates the determinations of acetone, acetoacetic acid, oxybutyric acid sugar, cholesterol and total fat content of the blood and the acetone, diacetic acid and sugar content of the urine. He also lists the results of the same hematologic determinations for 13 infants with livers of different sizes. Except for the children with diabetes, a single set of determinations was done for each child. These records are of use in fixing standards but do not seem to be subject to interpretation in themselves.

DOOLEY, New York.

GREEN VEGETABLE FLOUR IN INFANT FEEDING. G. M. TOSATTI, Lattante **9**:341 (Aug.) 1938.

Green vegetable flour was used in the feeding of several rachitic children between 6 and 8 months of age. Improvement was manifested by increased dentition, roentgen changes in the bones of the forearm and wrist and increase in the phosphorus content of the blood. Each 5 Gm. of the flour contained the equivalent of 5 Gm. of fresh spinach, 5 Gm. of fresh carrots and 5 Gm. of fresh tomatoes.

HIGGINS, Boston.

BLOOD TRANSFUSION FOR DYSTROPHIC INFANTS. A. IANCU and C. OPRISIU, Monatschr. f. Kinderh. **74**:209, 1938.

The writers find that blood transfusions increase the total nitrogen content of the blood as well as the polypeptids, while the albumin-globulin quotient sinks. In view of these findings one must beware of indiscriminate blood transfusion.

GERSTLEY, Chicago.

ALIMENTARY INTOXICATION IN THE FIRST THREE MONTHS. W. BAYER, Monatschr. f. Kinderh. **75**:177, 1938.

Bayer presents an excellent description of the symptoms and treatment of alimentary intoxication of the type described by Finkelstein some thirty years ago.

GERSTLEY, Chicago.

Oil Milk. G. Frontali, Monatschr. f. Kinderh. **75**:189, 1938.

Frontali describes a synthetic mixture in which fat is supplied in the form of olive oil. He claims good results from its use. Gerstley, Chicago.

Feeding of Irradiated Fresh Milk Over Long Periods. K. Scheer, München. med. Wchnschr. **85**:1396 (Sept. 2) 1938.

Irradiated milk is the best prophylactic and curative antirachitic agent available. However, because some physicians have felt that it may be harmful when given over a prolonged period, it has not been used in certain parts of Germany. The possible harmful effects were studied by Scheer. He fed several hundred infants and children irradiated fresh milk for periods ranging from three months to over two years. The patients were carefully observed clinically, and electrocardiographic and roentgenologic examinations of some of them were carried out. No harmful effects were found. Brahdy, Mount Vernon, N. Y.

Vitamins; Avitaminoses

Vitamins in Relation to Gastro-Intestinal Diseases. M. G. Vorhaus, Am. J. Digest. Dis. **5**:405 (Sept.) 1938.

Vorhaus calls attention to the so-called subclinical state of avitaminosis as seen clinically. The condition may be brought on by disease as well as by faulty diet.

The dietary sources of the different vitamins are reviewed. The daily adult requirement of vitamins is given. Morrison, Savannah, Ga.

Role of Vitamin C in Metabolism of Nerve Tissue. H. Wortis, S. B. Wortis and F. I. Marsh, Arch. Neurol. & Psychiat. **39**:1055 (May) 1938.

Vitamin C is present in relatively high concentration in nerve tissue. The cortical gray matter of the scorbutic guinea pig contains a third to a sixth as much ascorbic acid as does that of the normal animal. An alcoholic person with peripheral neuritis or mental disturbance due to alcoholism has a subnormal vitamin C content of the blood and cerebrospinal fluid. The authors feel that vitamin C plays a role in the metabolism of nerve tissue. Beverly, Chicago.

Intradermal Dye Test for Vitamin C Deficiency. H. G. Poncher and C. H. Stubenrauch Jr., J. A. M. A. **111**:303 (July 23) 1938.

The authors found that they were unable to confirm the findings of Rotter and those of Portnoy and Wilkinson with an intradermal dye test for the determination of vitamin C. The studies of Poncher and Stubenrauch were carried out on patients with clinical scurvy, patients whose blood showed a low content of vitamin C and patients whose blood showed a normal content of this vitamin. Checking each test with determinations of the ascorbic acid content of the blood, they found that there was overlapping in the time necessary to decolorize the dye in the skin. They feel that the dye is probably decolorized by other reducing agents in the skin. Heersma, Kalamazoo, Mich.

Vitamins in the Nutrition of Children. D. Vickery, M. J. Australia **2**:225 (Aug. 13) 1938.

This article is simply a review of vitamin deficiencies. Attention is called to some of the materials used in supplying vitamins. Tenney, Madison, Wis.

EXISTENCE OF ENDOGENOUS VITAMIN IN THE ANIMAL ORGANISM. L. MAGNI, Arch. ital. di pediat. **5**:454 (Oct.) 1937.

Aqueous extracts of the livers of rats deprived of vitamin C for more than a year when administered to guinea pigs fed a scorbutic diet impeded the manifestation of symptoms but once the scorbutic syndrome was manifest did not bring about cure. Similar results were obtained with extracts of the livers of rats fed with scorbutic diets for two and three generations.

Extracts from the stomachs, livers or kidneys of rats which had been given a rachitogenic diet for twelve to fourteen months resulted in cure when introduced into the diet of immature rats with experimental rickets.

The author interprets his experiments as showing the capacity of the animal organism to synthesize vitamins C and D. DOOLEY, New York.

INFLUENCE ON THE GROWING ORGANISM OF ULTRAVIOLET IRRADIATION IN CONNECTION WITH VARIOUS DIETS. H. BISCHOFF, Monatschr. f. Kinderh. **73**:300 (June) 1938.

Rats given a minimum diet respond to ultraviolet irradiation with an increase in weight. Those fed a full diet are uninfluenced. Rats given a minimal diet as compared with rats given an optimal diet show estrus in a frequency ratio of 6 to 14. The ultraviolet rays increase the frequency for animals given a minimal ration but do not affect the well nourished animals. Fertility is unaffected by irradiation. GERSTLEY, Chicago.

PELLAGRA AND THE NERVOUS SYSTEM. E. GLANZMANN, Monatschr. f. Kinderh. **74**:48, 1938.

Glanzmann reports the case of an 11 year old boy with typical pellagra. Photographs show the cutaneous lesions appearing predominantly over the knees. The symptoms referable to the nervous system consisted of heightened emotional reaction, hypertonia, hyperkinesis and ataxia. The usual stomatitis and swelling of the mucosa were present.

The treatment consisted of indiscriminate use of all accessory food factors. The boy was given hydrochloric acid with pepsin, yeast, liver preparations and stomach preparations. Recovery was dramatic. GERSTLEY, Chicago.

ANTIRACHITIC EFFECT OF VITAMIN D-3. P. STEINBRÜCK, Monatschr. f. Kinderh. **74**:185, 1938.

The effect of crystalline vitamin D_2 was contrasted with that of vitamin D_3 obtained from an extract of fish liver oil. With 34 infants there was no difference in the effect of the two vitamins as shown by the calcium and phosphorus content of the blood, the roentgen appearance of the carpal bones, and the clinical manifestations. GERSTLEY, Chicago.

Hygiene; Growth and Nutrition; Public Health

NEGLECTED HEALTH FACTORS IN PUBLIC SCHOOLS. W. ROSENSON, New York State J. Med. **38**:7 (Jan. 1) 1938.

The New York city schools are again accused of breaking down the physical and mental health of children through conditions, methods and customs which are definitely harmful and require revision. Rosenson, medical adviser to the health committee of the United Parents Association, New York, cites cases to prove his points.

New York has the shortest lunch period of any large city in this country. Children do not have adequate time to eat. It is suggested that the fifty minute period should be changed to one and one-quarter hours.

The campaign for full attendance is so keen that children will not stay at home when they are ill and so expose others to disease and themselves to greater risks. Forced attendance is to a large extent brought about because the state makes a reduction in its financial aid for every day a child is absent. It is urged that the competition for 100 per cent attendance records be abolished.

That New York should be so backward in providing modern toilet facilities for its children is astonishing. "According to a recent survey by the Health Committee of the United Parents Association in only fourteen schools of fifty-one visited did the lavatories conform to modern standards. Nineteen still had the old-fashioned outside toilets, some without even a connecting shed to the main part of the building. Seats are of the 'old square wooden type painted a dingy gray.' There is no adequate equipment for washing the hands. No soap or towels are provided. Some schools have no wash basins."

Excessive homework is criticized, also the fact that there are too many students per teacher. Finally it is suggested that courses in mental hygiene be made compulsory for every teacher.

AIKMAN, Rochester, N. Y.

INFANT MORTALITY IN BRITISH INDIA. K. C. BASAK, Indian J. Pediat. **5**:145 (July) 1938.

The infant mortality rate in British India ranks among the highest in the world. Furthermore, during the period from 1926 to 1935 there was no indication of reduction in the rate, which for 1934 was 187 per thousand of population. Different parts of India vary tremendously in regard to infant mortality; the highest rate from 1926 to 1935 was 233 per thousand; the lowest, 137. Although infant mortality generally is not declining, neonatal mortality has shown some tendency to decline within recent years. Infant mortality in Bombay City is closely associated with overcrowding.

GONCE, Madison, Wis.

A PEDIATRIC CONSULTATION SERVICE IN RURAL AREAS. J. H. MASON KNOX JR. and MYRON E. WEGMANN, Bull. Assoc. internat. de pédiat. prévent. **5**:3, 1938.

The authors, officers of the Maryland state department of health, discuss in detail measures designed to bring to the rural physicians of the state information concerning such advances in the control of diseases of infancy and childhood as have been demonstrated to be of prime importance. This work serves to familiarize the general practitioner with modern technics without requiring him to leave his practice. The services of a pediatric consultant are offered without charge. The enterprise has met with a cordial reception, and the authors commend it for wider application.

AMESSE, Denver.

FIRST YEAR OF THE FUNCTIONING OF A WELL BABY CLINIC. F. BORSARELLI, Lattante **9**:333 (Aug.) 1938.

Statistics as to size, age, diet and abnormalities are given on 528 children seen during the first year of a well baby clinic in Turin, Italy.

HIGGINS, Boston.

ANNUAL SURVEY OF CHILD HYGIENE SERVICE. T. GUGLIELMINI, Prat. pediat. **16**:13 (Jan.) 1938.

The author briefly enumerates the medical services furnished in eight public schools and in numerous asylums and private institutions. These services range from routine inoculation against diphtheria and smallpox to placement of children in special convalescent and corrective institutions. They concern children with all varieties of conditions, from acute infectious disease to problems of delinquency.

DOOLEY, New York.

COLLABORATION IN SCHOOL HYGIENE. T. GUGLIELMINI, Prat. pediat. **16**:67 (March) 1938.

This is a continuation of the author's report of his experience in the Milan schools (*Prat. pediat.* **16**:13 [Jan.] 1938), with particular reference to the role of the teacher in the prophylaxis of infectious disease, the management of contagion and the rendering of first aid. The subject receives no new treatment. A good bibliography of the Italian literature on school hygiene accompanies the article.

DOOLEY, New York.

SCHOOL HEALTH IN THE MODERN ERA. T. GUGLIELMINI, Prat. pediat. **16**:241 (Aug.) 1938.

Guglielmini completes his series of articles on school health (*Prat. pediat.* **16**: 13 and 67, 1938) with this hortatory discourse on the social opportunities in the modern practice of medicine in schools.

DOOLEY, New York.

WHEN SHOULD LEGISLATIVE MEASURES OR PUBLIC ORGANIZATIONS REPLACE THE LACK OF PARENTS? R. JALABERT, Bol. Inst. internac. am. de protec. a la infancia **12**:259 (Oct.) 1938.

The juridical standard and public organizations should always interfere when the father and mother are physically or morally, totally or partially unable to give the minor child all the corporal and spiritual aid his situation requires.

LESLIE, Evanston, Ill.

PROTECTION OF CHILDREN IN LATVIA. J. AKMENS, Pro juventute **1**:5 (June 12) 1937.

This is a presentation of the various agencies which are concerned with child welfare in Latvia. The state provides medical care for children and for mothers during pregnancy and delivery and provides material necessities when there is actual want. It also supervises the placing of dependent children and the arrangements for adoption of such children. The private agencies are concerned mostly with providing outings in the country for these children and developing and improving facilities for play.

LESLIE, Evanston, Ill.

PUBLIC AID IN LITHUANIA. A. HUNEBELLE, Pro juventute **1**:21 (June 12) 1937.

This is a presentation of the agencies for administering to maternal and child welfare in Lithuania. It also includes general proposals for the improvement of the laws on this subject.

LESLIE, Evanston, Ill.

PHYSICAL DEVELOPMENT IN CHILDREN UP TO TWO YEARS: A STUDY OF MATERIAL COLLECTED IN WELFARE STATIONS. R. BARANSKI, Pediatria polska **18**:53 (Feb.) 1938.

Up to 1938 Poland did not have her own statistical data on physical development in children up to 2 years of age. Physicians and medical students had to use measurements and data on physical development from other nations. This was not justifiable, because children of other nationalities or races live in different circumstances and present different types of development. This compelled Baranski to direct research along these lines. Part of the work was inaugurated by Dr. J. Bogdanowicz. The clinical material that has been accumulated in the department of children's diseases at the University of Pilsudski prompted Baranski to pursue this type of work where he has conducted the children's clinic for the

last fifteen years. His material comprises only healthy non-Jewish children of both sexes up to 2 years of age. For statistical data reference may be made to the article.

KRUPINSKI, Chicago.

Prematurity and Congenital Deformities

REPORT ON TWO CASES OF CLEIDOCRANIAL DYSOSTOSIS. H. R. COOPER, Am. J. Orthodontics **24**:843 (Sept.) 1938.

Cooper observed 2 patients with this deformity, one a girl of 15 and the other a boy of 11 years. From a dental standpoint the condition results in delayed eruption of teeth and seemingly affects only those teeth that have deciduous predecessors. What one can do from an orthodontic standpoint to help the teeth erupt is still not determined.

FROM LEWIS, Dayton, Ohio. [ANGLE ORTHODONTIST]

HEREDITARY MALFORMATION OF VERTEBRAL BODIES. S. JARCHO and P. M. LEVIN, Bull. Johns Hopkins Hosp. **62**:216 (March) 1938.

This paper presents clinicopathologic reports on 2 children (sister and brother) with severe malformation of the bodies of the cervical and thoracic vertebrae. Other anomalies were present as well in another sibling and in the mother.

The symptoms may be divided into two groups: 1. Those dependent on the cervical deformity constitute the Klippel-Feil syndrome of short neck, limited mobility and low hair line. 2. As a result of the thoracic malformation, the chest was short and convex anteriorly, and the abdomen bulged; this produced impairment of pulmonary ventilation, fatal at an early age.

In the inheritance of the Klippel-Feil deformity there appear to be two factors: a general dysplastic factor, producing various types of anomaly, and a specific factor, producing the vertebral defect, which may be almost identical in the affected members.

One of the patients described here had a numerical reduction of the spinal nerve roots corresponding to the decrease in number of vertebrae. This demonstrates that the so-called segmentation of the spinal cord really depends on extrinsic structures rather than on a fundamental pattern within the nervous system.

AUTHORS' SUMMARY.

CASE OF SIAMESE TWINS, COMPLICATED BY ECLAMPSIA. M. I. EALING, J. Obst. & Gynaec. Brit. Emp. **45**:79 (Feb.) 1938.

The author reports the delivery without embryotomy of a double monster of the type thoracopagus. Both members were female. There was a single cord. Postmortem examination was not performed.

ADAIR AND POTTER, Chicago.

GARGOYLISM. R. W. B. ELLIS, Proc. Roy. Soc. Med. **31**:770 (May) 1938.

Ellis reports the case of a girl aged 1 year and 8 months. She was taken to the hospital on account of mental retardation. She could not sit up alone, made no attempt to stand and could not feed herself, speak or control her excretions. Complete data on the physical examination and all investigations are given in the report, which is illustrated with pictures of the patient. The characteristic features of gargoylism (the peculiar facies, mental deficiency, cranial deformity, corneal opacity, hepatosplenomegaly and kyphosis) were present, and the bone changes, though not marked or universal, were those of osteochondrodystrophy. The pituitary fossa did not show the enlargement seen in many cases.

WILLIAMSON, New Orleans

ELECTROCARDIOGRAPHIC INVESTIGATION OF PREMATURE AND FULL TERM NEWBORN INFANTS. V. MIGLIORI, Arch. ital. di pediat. **6**:176 (April) 1938.

The electrocardiograms of 21 premature and 23 full term babies taken in the neonatal period were analyzed, without demonstration of significant differences in the two groups.

DOOLEY, New York.

BRINGING UP OF PREMATURE INFANT. N. CARRARA, Lattante **9**:21 (Jan.) 1938.

Only 5 deaths occurred among 39 premature infants cared for during the past five years in the Asilo-Nido "Duchessa Anna d'Aosta" in Gorizia, Italy. Breast milk composed all or a part of the diet of most of the infants. Insulin, an estrogen and the serum of gravid women were of therapeutic value in this group. Blood transfusions were more useful in preventing anemia than administration of iron, copper and manganese. Proper feeding, regulation of heat, avoidance of hospital infections and, above all, the attention of well trained nurses are the important factors in bringing up premature infants.

HIGGINS, Boston.

CHONDRODYSTROPHIA FETALIS. M. MEISGEIER, Monatschr. f. Kinderh. **74**:110, 1938.

Seven cases are reported, with the usual pathologic anatomic changes. Attention is called to incidental findings, such as hydrocephalus, funnel breast and rickets. In 2 other cases there was what the writer calls borderline involvement; he presents roentgenograms taken in these cases, indicating abortive and atypical forms of the disease, and he labels this condition "achondroplasia fruste."

As regards sterilization of patients with fetal chondrodystrophy, each case must be considered individually.

GERSTLEY, Chicago.

Newborn

OPHTHALMIA NEONATORUM AND GONORRHEAL AFFECTIONS OF THE EYES OF CHILDREN. C. BERENS, Arch. Pediat. **55**:639 (Oct.) 1938.

Ophthalmia neonatorum accounts for 7.1 per cent of admissions from 1932 to 1936 inclusive to schools for the blind in the United States.

A certificate of freedom from gonorrhea before marriage should be required in every state.

Routine bacteriologic diagnosis should be made in all cases in which there are symptoms of ophthalmia neonatorum, and treatment should depend on the cause.

Treatment with foreign protein has proved beneficial. Sulfanilamide seems to be efficacious.

Because gonorrheal conjunctivitis occurs in children and may cause blindness, every measure for prevention and treatment of gonorrhea in children should be employed.

ORR, Buffalo.

EPIDEMIC OF MOUTH INFECTION OF NEWBORN. L. H. DOUGLASS, J. Pediat. **12**: 323 (March) 1938.

Douglass describes an epidemic of oral infections which spread rapidly among the newborn in a nursery for white and one for Negro children, 46 of a total of 50 babies becoming infected within six days. Despite all the normal precautions of isolation, the epidemic was controlled only by closing the obstetric division and nurseries and cleaning, sterilizing and airing them for ten days. The incubation period was difficult to determine. One baby showed involvement when it was but 36 hours old, and one baby seemingly had been exposed for seven days before it was infected. Another baby was discharged well and readmitted thirty hours later with extensive involvement. In almost all instances the first symptom noted was an excessive secretion of mucus, which in some cases required aspiration. After

this the mucous membrane of the soft palate, particularly that portion near its junction with the hard palate, was seen to be reddened but not swollen; a few hours later, it was covered with an almost pure white membrane. The membrane could be separated from the underlying mucosa with difficulty, and the mucosa was then seen to be reddened, but it did not bleed from the line of cleavage. Most of the babies did not appear ill and after about ten days appeared perfectly well again. Seven of the babies showed pharyngeal involvement by extension, which caused some cyanosis and interfered with swallowing. These babies appeared dehydrated and had low grade fever and some diarrhea. Two coughed up definite casts of the trachea, 5 to 7 cm. long, and almost immediately showed definite clinical improvement.

The mortality was zero. In spite of the fact that these babies nursed at the breast and several of the mothers had cracked nipples, no mammary infection occurred. The babies were treated first with sodium perborate, then with aqueous and later with alcoholic gentian violet. The treatments seemed to be ineffectual, and finally no treatment was given, and recovery seemed to be accelerated. Smears and cultures were made, but no one organism was found to be present in all cases. Vincent's bacillus was not found, nor any of the fungi that cause thrush. No chemical or mechanical irritation was discovered to be the cause.

RAUH, Cincinnati.

HEMORRHAGIC DISEASE OF THE NEWBORN IN THREE SUCCESSIVE INFANTS OF ONE FAMILY. F. HALL, New Rochelle Hosp. Bull. **1**:28 (June) 1938.

The first infant to show hemorrhagic symptoms in the family observed by Hall was the result of the fourth pregnancy. At birth this child showed generalized purpura but the platelet count and the bleeding and coagulation time were normal. Twenty cubic centimeters of blood was given immediately by the intramuscular route, but on the fourth and the eighth day the child showed bleeding from the upper and the lower portions of the bowel, and an intracranial hemorrhage occurred. Intravenous transfusions apparently saved life, but the child became an idiot, showing a communicative type of hydrocephalus. The second child showed a purpuric rash at birth with a platelet count of 113,000 and a prothrombin quotient of 0.7. The bleeding and coagulation time were normal. Blood was given immediately by the intramuscular route, followed by two intravenous transfusions. The child developed normally. The third child showed a similar purpuric rash, with a platelet count of 20,000, a bleeding time of fifteen minutes and a coagulation time of four and a half minutes. There was no clot retraction in twenty-four hours. Blood was given immediately by the intramuscular route, and intravenous transfusion was given when the child was 2 days old. On the tenth day the platelet count had increased to 49,000.

The reviewer questions the validity of considering all these cases as instances of hemorrhagic disease in the newborn. The third case in particular seems definitely to be one of thrombopenic purpura.

It is interesting to note that the blood given intramuscularly to the first child did not prevent severe hemorrhage. In the other 2 instances, intravenous transfusions were given early and may have been a factor in preventing severe hemorrhage.

LESLIE, Evanston, Ill.

SUBCUTANEOUS EMPHYSEMA IN THE NEWBORN. G. SLOT and W. D. BROWN, Brit. J. Child. Dis. **35**:116 (April-June) 1938.

The occurrence of subcutaneous emphysema without trauma in the newborn child is extremely rare.

Theories as to its possible cause include intrauterine attempts at respiration followed by penetration of air to the surface through the anterior mediastinum, increased intra-alveolar pressure caused by artificial inflation of the lungs after birth, and violent coughing.

The authors cite an instance of pronounced subcutaneous emphysema of the neck and the upper portion of the chest, the patient being a newborn infant delivered by a midwife. It was reported that while the infant's face was still within the vulval outlet sucking noises were heard, as though the child were trying to breathe.

The treatment of the condition is rest and careful nursing. Administration of oxygen seemed to help in the case cited.

The prognosis is usually good if the condition is uncomplicated, and recovery is complete in six to fourteen days. LANGMANN, New York.

CAUSE AND TREATMENT OF CERTAIN CASES OF ASPHYXIA NEONATORUM. W. STANSFIELD, J. Obst. & Gynaec. Brit. Emp. **45**:87 (Feb.) 1938.

In stillborn infants disappearance of fetal cardiac tones late in the course of labor is usually due to excessive accumulation of fetal blood in the placenta and consequent lack of blood in the body of the fetus. After the fetus is delivered, if the cord is grasped close to the vulva and the blood present in the cord milked back into the infant, the cord released, blood allowed to accumulate in it and this in turn forced into the body of the fetus, and the process repeated several times, the heart of the fetus, in many cases, will commence beating again. This is the most efficient method the author has discovered for treating asphyxia neonatorum.

ADAIR AND POTTER, Chicago.

HEMOGLOBIN CHANGES IN CASES OF NEONATAL ICTERUS. F. RASI and M. BIANCHI, Arch. ital. di pediat. **5**:533 (Dec.) 1937.

The authors made frequent erythrocyte counts, hemoglobin determinations and quantitative estimations of fecal bilirubin during the first and second weeks of life in 21 normal infants, 10 of whom had no demonstrable icterus and the remainder of whom were definitely jaundiced. In all instances the excretion of bilirubin presented an ascending curve until the third to the fifth day, after which it tended to return to a normal value. The maximum excretion of bilirubin was generally below 50 mg. per hundred cubic centimeters in infants with jaundice. The maximum excretion could be roughly correlated with the extent of the fall in the erythrocyte count. Icterus neonatorum is considered to be hemolytic and to be an exaggeration of a physiologic phenomenon. DOOLEY, New York.

ESTIMATION OF THE AGE OF NEWBORN AND PREMATURE INFANTS FROM CHARRED BONES. G. SCHRÄDER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:152, 1938.

The research material consisted of the bodies of 16 children close to maturity, weighing from 1,340 to 3,480 Gm. and measuring from 34 to 56 cm. in length. One half of each body was burned; the other half was macerated. In this manner comparable material was acquired for measurement. It was found that burned bones were shorter than those that were macerated. The bones had shrunk also in other dimensions, so that estimates of the age of the child might be as much as one to two months in error. Thus it was found that the macerated bones of a child 45 cm. long were slightly larger than the burned bones of a child 50 cm. long.

RUKSTINAT. [ARCH. PATH.]

PHRENIC PARALYSIS IN CHILDREN AS A RESULT OF TRAUMA SUSTAINED AT BIRTH. R. SOBOLEVITSCH, Jahrb. f. Kinderh. **147**:86 (July) 1936.

Numerous case histories are given. The cases are divided into two groups: (1) cases of paralysis of the phrenic nerve associated with other types of paralysis, such as associated paralysis of the arm, and (2) cases of paralysis of the phrenic nerve alone.

The possibility and probability of bouts of pneumonia following injuries of this type are discussed. The prognosis is dependent on the severity of the injury. If healing occurs, it usually takes place within nine months.

LANDAU, Hannibal, Mo.

HEMORRHAGE FROM SUBCUTANEOUS CEPHALHEMATOMA ENDANGERING BABY'S LIFE. G. SCHÄFER, Ztschr. f. Geburtsh. u. Gynäk. **116**:318 (Feb.) 1938.

A newborn infant almost died of hemorrhage from a subcutaneous cephalhematoma and was saved only by a suture covering the hematoma with a fold of skin. No report of a similar case was found in the literature.

ADAIR AND LANDÉ, Chicago.

Acute Contagious Diseases

CHICKENPOX MENINGITIS AND ENCEPHALITIS. O. L. FAUST, Arch. Pediat. **55**: 29 (Jan.) 1937.

Three cases of chickenpox are reported in which there were cerebral complications: meningitis in 1 and encephalitis in 2. In all cases the recoveries were uneventful, with no sequelae.

ORR, Buffalo.

EXPERIMENTAL POLIOMYELITIS BY THE TONSILLOPHARYNGEAL ROUTE. A. B. SABIN, J. A. M. A. **111**:605 (Aug. 13) 1938.

The occurrence of poliomyelitis following tonsillectomy and the high incidence of the bulbar type of the condition led to the author's experimental work on monkeys.

Several controlled procedures of intranasal and pharyngeal application and intratonsillar injection of the virus, some of which were followed by tonsillectomy, led to the following conclusions: The tonsillar area is more susceptible to inoculation with virus than are most subcutaneous and submucous areas. Entry of the virus takes place along the peripheral (cranial) nerves, and bulbar poliomyelitis is extremely prone to develop. The trauma of tonsillectomy may be a factor in introducing the disease. The virus is perhaps most prevalent in summer.

HEERSMA, Kalamazoo, Mich.

EAR COMPLICATIONS OF SCARLET FEVER. A. L. HOYNE and R. SPAETH, J. Pediat. **12**:287 (March) 1938.

The aural complications of scarlet fever are so frequent and so serious that their importance should be appreciated more fully by members of the medical profession. A study was made of the aural complications among 3,564 patients with scarlet fever treated at the Municipal Contagious Disease Hospital in Chicago from July 1, 1934, to June 30, 1935. Tables are presented showing the data on the incidence of otitis media among these patients in comparison with similar data taken from the literature. The incidence of mastoiditis, the number of mastoidectomies done, the mortality, and the complications of mastoid disease among the 3,564 cases are also given in tabular form. Other tables included in this report show the week of onset of purulent otitis media, the incidence according to age and the importance of this complication as a cause of death.

The authors suggest certain therapeutic measures which would in all probability have a distinct influence on the incidence of otitis media. General supportive measures, such as blood transfusions, parenteral administration of fluids, adequate diet and effective sedative therapy, appear to increase the patient's resistance to infections of the middle ear and mastoid. Maintenance of unobstructed nasal passages is essential to the prevention of mechanical spread of septic material from the nasopharynx through the eustachian tubes to the middle ear. Irrigations of

the throat and gargles are to be avoided. In hospital wards patients with uncomplicated scarlet fever should be separated from those with complications, and protection from cross infections is essential. Care must be taken to resort to paracentesis only when necessary, and the operation should be done by an otologist or a competent physician. Irrigations of draining ears have not been done at the Municipal Contagious Disease Hospital during the past eighteen years, but recent reports in the literature on the beneficial action of irrigation with alcohol have been encouraging, and the procedure may be useful. A strict aseptic technic is essential in the care of the draining ear. It is suggested that adenoidectomy be done on patients with otorrhea, in order to decrease the duration of the aural discharge and avoid incriminating invasion of the mastoid cells as a cause of prolonged aural discharge.

RAUH, Cincinnati.

IMMUNOLOGIC APPLICATION OF PLACENTAL EXTRACT. C. F. MCKHANN, New England J. Med. **216**:450 (March 18) 1937.

The development of placental extract for immunologic use is the outgrowth of a search for a more satisfactory method of controlling measles. The dosage of placental extract, as well as that of convalescent serum or of adult blood, is influenced by several factors, notably the potency of the extract, the time of administration, the age and size of the patient and the degree of exposure.

The administration of placental extract intramuscularly is followed in some instances by a local or a general reaction; only 6 per cent of the patients suffered a local reaction that was classed as moderately severe, and in only 3.1 per cent did the temperature go above 101 F.

Injections of placental extract have not been found to sensitize to subsequent injections of the material. Immunity following the injection of placental extract, like that following the use of convalescent serum, is passive in type and of short duration.

GENGENBACH, Denver.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:247 (Feb. 18) 1937.

For the period of Jan. 2 to 29, 1938, the number of cases of measles rose to 71,000. This was four times that of the previous two years. All areas were affected except the New England region. The incidence of smallpox, meningitis and scarlet fever was also slightly above the median. That of diphtheria, poliomyelitis, typhoid and influenza was below the median. The average mortality was 12.6 per thousand, which is below the average. SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:1733 (Sept. 30) 1938.

From August 14 to September 10 the incidence of influenza was slightly above normal, while that of smallpox, which has been very high, dropped to a lower level. Poliomyelitis, scarlet fever, diphtheria, measles, meningitis and typhoid were below the normal level. The average mortality was 9.7 per 1,000, which is normal.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:1907 (Oct. 28) 1938.

For the period from September 11 to October 8, 1938, the number of cases of influenza increased to 2,653, about 35 per cent above the level of 1937. The incidence of smallpox decreased but was still above the average, as was that of measles. The incidence of poliomyelitis, meningitis, typhoid, diphtheria and scarlet fever was below the median. The mortality from all causes was 10.2 per 1,000 of population. This is slightly above the average for this period.

SANFORD, Chicago.

Measles in the Sayeda Zenab Foundling Home, Cairo, Egypt. A. Bey Fouad, J. Egyptian M. A. **21**:393 (June) 1938.

During three outbreaks of measles in the Sayeda Zenab Foundling Home in the years 1931, 1933 and 1936, (*a*) 22 children had measles twice, 6 of them in the same year; (*b*) 5 children had the disease three times; (*c*) there was no special seasonal incidence, and (*d*) the mortality rate was 30 per cent.

Mulherin, Augusta, Ga.

Bacteriophage in the Treatment and Prophylaxis of Cholera. W. Omar, J. Egyptian M. A. **21**:491 (Aug.) 1938.

This paper is a rather extensive review of the literature on this subject. It is not original. From the review the following conclusions are drawn: 1. The experiments carried out are unfortunately liable to criticism. 2. The results given in the different reports are not clearcut and are contradictory. 3. The results obtained from 1928 until the present time do not permit consideration of bacteriophage as a substitute for the curative and preventive measures now in use. 4. Bacteriophage has a certain value in the treatment and prophylaxis of cholera, as it seems to lessen the mortality rate.

Mulherin, Augusta, Ga.

Preliminary Survey of the Types of Corynebacterium Diphtheriae Isolated at the Metropolitan Infectious Diseases Hospital, Northfield. M. C. Puckey, M. J. Australia **1**:851 (May 14) 1938.

Sixty-eight pure cultures were obtained and typed; 32 were "gravis" and 36 were "mitis" forms. The "intermediate" form was not encountered. "Gravis" infections were severer than "mitis," responded poorly to antitoxin and were more favorable to the development of complications, so that convalescence was protracted. There were 5 deaths among the patients with "gravis" infections and 2 among the patients with "mitis" infections. Of the 68 cultures typed, 4 (3 "mitis" and 1 "gravis") were obtained from children who had received three immunizing injections of anatoxin three to eighteen months previously.

Gonce, Madison, Wis.

Preliminary Observations on the Virus Responsible for the Victorian and Tasmanian Epidemics of Poliomyelitis. F. M. Burnet and E. V. Keogh, M. J. Australia **2**:130 (July 23) 1938.

The authors isolated a typical strain of the virus of poliomyelitis from the spinal cords of several patients who died during the Victorian and Tasmanian epidemics of poliomyelitis in 1937. They found this strain to have a significant antigenic resemblance to the classic strain MV of the Rockefeller Institute for Medical Research, but not to be identical with it.

Gonce, Madison, Wis.

Diagnosis of Poliomyelitis. M. L. Powell, M. J. Australia **2**:276 (Aug. 20) 1938.

Powell reports observations based on 488 cases of epidemic poliomyelitis. The paralytic phase, if it appears at all, always follows the febrile phase, and a reversal in these phases argues against the diagnosis of poliomyelitis. The disease may be classified into six main varieties: the hypothetic type (undiagnosable); the undiagnosable type followed by slight paralysis; the abortive type; the "dromedary type;" the classic type, and the classic type without paralysis (nonparalytic poliomyelitis).

Fever is uniformly present. Drowsiness is slightly less constant than fever and is of a character that permits the child to be alert, lucid and cooperative when aroused. Stupor is rare. Headache is common; it is usually frontal or supraorbital and often intermittent. Nausea, vomiting (once or twice) and

anorexia are common. Sore throat is an early symptom in many cases. Pain in the form of a dull ache in the back of the neck and in the back is probably the symptom that should arouse the most suspicion; it is present in 80 per cent of cases. Abdominal pain is present in about 30 per cent. Muscular pain and hyperesthesia early in the course of the disease are not nearly so common as might be expected. Tremor is of the intention type and if present is almost pathognomonic. Jactitation, a single coarse spasm of a limb or of the whole body, occurs fairly commonly, usually during sleep and particularly in patients with tremor. Disturbance of micturition occurs in the form of difficulty in starting the act or complete inability to urinate. Mild constipation is common, and diarrhea is rare. Photophobia, squint and diplopia are rare. Epistaxis occurs occasionally. Vocal symptoms, if present, are very significant.

As to physical findings, the spinal signs are the mainstays of diagnosis. Stiffness of the neck is the sign most uniformly present. It may be elicited either by gently flexing the neck of the completely supine child or by directing the child seated on the bed or on the mother's knee to look at a flash light held near his umbilicus. No matter how stiff the neck may be to anterior flexion, lateral rotation of the head from side to side is extraordinarily painless—an important differential diagnostic sign with regard to fibrositic, traumatic or inflammatory conditions in this region. Again, no matter how stiff are the neck and back, palpation elicits comparatively little tenderness. The best test for stiffness of the spine is kissing the knees. This may be attempted while the child sits in any position he chooses or lies on his side. Amoss', or the tripod, sign, caused by a combination of weakness of the truncal muscles and spinal rigidity, is not commonly seen in the early stages of the disease. Head lag, demonstrated by slowly raising the shoulders of the supine child without supporting the head, is a test for weakness of the flexor muscles of the neck and is unusual in the early hours of the disease. Kernig's sign is rarely of any great help when it is positive, the other signs of cervical and spinal stiffness are also present and are much easier to confirm. Asymmetric diminution of reflexes is significant.

Certain findings in the history or on examination argue against the diagnosis of poliomyelitis. Cough, with or without coryza, is extremely unusual except in severe bulbar poliomyelitis and in the presence of purely coincident infection of the respiratory tract. Diarrhea, severe pain and tenderness in any region of the body, mental clouding, convulsions and rash are all unusual. The spleen is practically never palpable in poliomyelitis, and the finding of an enlarged spleen in this disease indicates the presence of some other infection.

In at least 90 per cent of cases poliomyelitis can be diagnosed without lumbar puncture. Data on the cerebrospinal fluid after the disease has become well established merely confirm the clinical diagnosis. In the first six to eighteen hours of the disease (a time when diagnostic help is most wanted) the cerebrospinal fluid is often normal. As a differential diagnostic procedure lumbar puncture is sometimes of great value.

GONCE, Madison, Wis.

ADVENT AND PROGRESS OF EPIDEMIC OF INFANTILE PARALYSIS ON ISLAND IN BRITISH SOLOMONS GROUP. C. S. JAMES, New Zealand M. J. **37**:32 (Feb.) 1938.

This is an interesting report of the spread of an epidemic of infantile paralysis among natives of an isolated island.

For more than a year an epidemic of infantile paralysis had been raging on all the islands of the British Solomons with the exception of one island of some 4,000 inhabitants. On this island the medical officer (the author) was maintaining a vigorous refusal of contacts with the outside world. On August 8 a government yacht with a native crew anchored off the island. Against orders, as was learned later, some of the crew secretly attended a church service on the island. Forty-eight to sixty hours later the first case of infantile paralysis occurred in a

native male who had attended the service. The next day a child came down and two or three days later an older girl. This girl lived in a different village, but it was found that a Chinese trader with a native crew had been there some forty-eight hours before. During the following four weeks there were several more cases, with 2 deaths. After that there were no more cases up to the time, two years later, when the author left the islands.

MULHERIN, Augusta, Ga.

ACUTE INFECTIOUS DISEASES. W. GUNN, Practitioner **141**:395 (Oct.) 1938.

No notable advance in the diagnosis of acute infectious diseases has been recorded in the last few years, although mechanical improvements in the performance of specific tests and wider experience with their interpretation have increased their value and range in many instances (notably the recent modifications of the Widal reaction for enteric fever and the cough-plate method for whooping cough). In the sphere of therapeutics, sulfanilamide and allied substances have dominated the situation; with the exception of typhoid fever, every important infectious disease has been alleged to respond in greater or less degree to these drugs. Even in cases of diphtheria sulfanilamide has been used if an accompanying or superadded streptococcic infection was suspected or proved by the cultural findings. Few clinicians have been bold enough to raise a dissentient voice against the almost universal acclamation with which this new drug has been received. The few doubters have tended to question the accuracy of their observations or have viewed with misgiving the paucity of their tests and the absence of proper controls. The favorable evidence has appeared to be overwhelming, but it is often forgotten that usually only successful experiences are published.

GELSTON, San Francisco.

ALBUMINOCYTOLOGIC DISSOCIATION OF THE CEREBROSPINAL FLUID IN ACUTE ANTERIOR POLIOMYELITIS. G. PAISSEAU and J. L. GREENE, Arch. de méd. d. enf. **41**:489 (Aug.) 1938.

In reporting the occurrence of infantile paralysis in a girl aged 10, the authors discuss the differential diagnosis and relate how difficult it was to eliminate the so-called Guillain-Barré syndrome. The painful onset, the lack of precision in the appearances of paralysis, the early abolition of the tendon reflexes and particularly the dissociation of the cell content and the index of hyperalbuminosis in the spinal fluid pointed strongly toward this type of radiculoneuritis, with its favorable prognosis.

The evolution of the condition, however, with its usual residual symptoms, placed it definitely in the category of poliomyelitis. From a pathologic point of view it is difficult to accord supreme importance to a failure of the cell content and the albumin content of the cerebrospinal fluid to increase at the same level.

AMESSE, Denver,

BLOOD GROUPS AND POLIOMYELITIS. A. RUSNICOVA, Bull. Assoc. internat. de pédiat. prévent. **18**:10, 1938.

Rusnicova's article on blood groups and poliomyelitis comprises three parts.

I. In the first part she summarizes briefly the results of past research regarding the relation between the diffusion and virulence of the virus and the various exogenous and endogenous factors which influence them: race, climate, density of population, immunization, balance of the endocrine system and age. Special attention is given to the results of research dealing with relations between the constitutional factor (serologic differentiation, with stabilization of blood groups) and immunity against poliomyelitis and other epidemic diseases. She quotes particularly the work of Dungern and Hirschfeld, Hirschfeld and Brockman, Nowak, Grosten and Kassowitsch, Foa, Shaw, Thelander and Kilgariff and Jungeblut, Hatsky, and Blotevogel.

II. In the second part she describes the experimental and statistical research which she carried out in 1936, at the Bambino Gesù Hospital, in Rome, Italy, during an epidemic of poliomyelitis. Her aim was to determine the possibility of a correlation between the various blood groups and resistance to the disease.

The following points are treated:

1. The distribution by blood group and by sex of the patients observed. Here the distribution by blood group was similar to that noted by Jungeblut and Smith.

2. The difference between the distribution according to blood group of the patients and that of a number of healthy children. The difference noted was extremely slight.

3. The distribution according to blood group and age. This agreed with that generally noted.

4. The distribution according to blood group and evolution of the disease. This distribution did not confirm the idea that any one specific group enjoys serotherapeutic immunization.

5. The distribution according to blood group and place of origin. The author's observations differ from those made by other workers, the distribution according to blood group being almost equal in rural and urban cases.

6. The difference between the blood group distribution of the children and that of their mothers.

III. The third part summarizes the author's conclusions:

1. The results obtained differ from those of other workers. The facts noted and the statistics gathered do not support the idea that members of blood group B are relatively better able to resist the disease.

2. Conclusions may be superficial and mistaken (*a*) because the number of observations made is small—a circumstance that generally marks research work of this kind—and (*b*) because the methods of research, classification, comparison and generalization of results are necessarily defective. AMESSE, Denver.

ACTION OF SODIUM BICARBONATE ON MEASLES. T. SOMALOMA, Infancia **1**:31, 1937.

Somaloma reports the use of large doses, from 15 to 25 Gm., of sodium bicarbonate a day in the treatment of measles. The temperature declines to normal on the second or third day, the general condition of the patient is much better, the complications fewer and the convalescence shortened.

Sodium bicarbonate alkalinizes the blood and urine, favors cellular oxidation, stimulates the secretion of urine and augments the metabolism and decongestion of the liver. HERRON, Monroe, La.

CONDITIONS THAT CAN INFLUENCE COURSE OF JENNERIAN VACCINATION. D. GYÜRE, Lattante **9**:12 (Jan.) 1938.

Vaccination of infants by intranasal instillation of smallpox vaccine resulted in establishment of immunity. The generalized reaction was no greater than that following use of the usual cutaneous method. HIGGINS, Boston.

DIPHTHERIA CARRIERS. G. LODI, Méd. inf. **9**:193 (July) 1938.

Lodi classifies diphtheria carriers as primary and secondary. Primary carriers are called active if they are immune to diphtheria toxin; otherwise they are called passive. Active primary carriers may have sufficient or insufficient immunity for complete protection. Passive carriers may be in the incubation stage, may acquire immunity or may have tissues insensitive to the bacilli and toxin. Secondary carriers are those who have recovered or are convalescing from diphtheria.

Of 49 carriers in Lodi's hospital, 7 had positive Schick reactions; of these, 3 still had positive Schick reactions after the administration of anatoxin.

HIGGINS, Boston.

COMPARATIVE CLINICAL STUDIES OF THE BLOOD AND SPINAL FLUID IN CASES OF INFANTILE PARALYSIS. S. MOSCHINI and I. BIDDAU, Riv. di clin. pediat. **36**:834 (Sept.) 1938.

Observations were made on 34 patients with poliomyelitis, the sugar, the chloride, the protein and the alkali reserve in the blood and spinal fluid being determined. In the spinal fluid the albumin tended to reach its highest level on the fourteenth to the twentieth day of the disease. The sugar reserve was high in the presence of polioencephalitis, and the alkali reserve was lower than normal. No absolutely characteristic chemical content of the spinal fluid was observed in cases of poliomyelitis; certainly the protein content was of no diagnostic or prognostic value. There was no parallelism between the clinical picture and the chemical reports on the blood and spinal fluid.

HIGGINS, Boston.

OBSERVATIONS ON MEASLES IMMUNIZATIONS. F. BAZÁN and E. SUJOY, Arch. argent. de pediat. **8**:1205 (Dec.) 1937.

The authors give a history of the various methods that have been used for immunizations and describe the placental globulin extract which they have used. They give favorable opinions as to the efficiency of this extract, emphasizing early injections and the use of larger doses than those prescribed.

The authors warn against the old belief that measles is a benign infection which the child must have, preferably in infancy. The mortality rate, if accurately determined, is high.

SCHLUTZ, Chicago.

WHEN IS THE SPECIFIC TREATMENT OF DIPHTHERIA PATHOGENETICALLY INDICATED? F. H. HOERING, Med. Klin. **34**:352 (March 18) 1938.

Hoering argues that serum treatment of diphtheria should not be completely discredited. Although tissues already damaged cannot be benefited, further damage can be averted. Antitoxin is of much greater value prophylactically than curatively. However, as long as prophylaxis is based on the antitoxic principle only, the organism itself being disregarded, it cannot be reliable.

SIEMSEN, Chicago.

CAUSE AND AVOIDANCE OF MISSING OF DIAGNOSIS OF DIPHTHERIA. F. WEISER, Med. Klin. **34**:354 (March 18) 1938.

Three cases in which the diagnosis of diphtheria was missed clinically are described: (1) a case of nail injury to the foot, with a necrotic lesion, (2) a case of peritonsillar infiltration and (3) a case of pharyngeal inflammation for which medical aid was sought late because of arthritis. Weiser states that it is important to suspect diphtheria in cases of angina even without membrane and ulceration and in the absence of pus formation and also in cases of cutaneous wounds with necrotic, nonpurulent inflammation. The presence of pseudosepticemia with a relatively low temperature and absence of splenomegaly tends to make the diagnosis certain.

SIEMSEN, Chicago.

PROPHYLAXIS OF COMMUNICABLE DISEASE. H. KLEINSCHMIDT, Monatschr. f. Kinderh. **75**:224, 1938.

On the basis of personal experience Kleinschmidt sees little benefit from the isolation of carriers of meningococci during an epidemic. The finding of hemolytic streptococci in the throats of convalescents is of little value in the prophylaxis of scarlet fever.

In epidemics of diphtheria Kleinschmidt's first procedure is to isolate all patients who show any clinical symptoms. This rule is particularly applicable to school children. In institutions he advocates making cultures of material from the throats of patients, particularly patients with scarlet fever. Making cultures of nasal secretions is highly important.

The danger from discharged children to other members of the family is much less with diphtheria than with scarlet fever. However, the writer believes that with both these diseases, instead of relying on data obtained by cultures of material from the throat the physician should keep the patient in quarantine for a minimum period of four weeks.

GERSTLEY, Chicago.

EMBOLI IN DIPHTHERITIC CIRCULATORY DISTURBANCES. H. ZISCHINSKY, München. med. Wchnschr. **85**:1221 (Aug. 12) 1938.

Zischinsky discusses the occurrence of an unusual complication of diphtheria observed at the Wilhelmina Hospital in Vienna during the last twelve years. During this period embolism was observed in 14 of 14,000 cases of diphtheria. It occurred only in cases of pharyngeal diphtheria with extensive myocarditis, and in all cases it was fatal. The emboli were distributed as follows: in the cerebral arteries in 12 cases, in the brachial artery in 2 cases and in branches of the pulmonary artery in 3 cases. In some instances there were multiple localizations. All the patients had extensive myocarditis with mural thrombi. When a small piece of a thrombus broke off, embolism followed.

Zischinsky also presents protocols of cases in which the diagnosis of embolic occlusion was made clinically but was not confirmed at necropsy. In some there was no anatomic explanation for the symptoms; in others there was softening of the brain without apparent vascular injury.

BRAHDY, Mount Vernon, N. Y.

SEPSIS DUE TO DIPHTHERIA BACILLI. H. KASCHEL, Ztschr. f. Kinderh. **59**:437 (Feb. 8) 1938.

After discussing the literature, Kaschel describes a case in which indefinite general symptoms had been present for about a week. Culture of the blood revealed a pure growth of a diphtheria bacillus which corresponded to the typical diphtheria bacillus serologically, biologically and culturally. However, it was avirulent in animal experiments. Kaschel assumes that the bacillus was of low virulence for man also. The autopsy is reported in detail. A prominent observation was endocarditis ulcerosa.

SIEMSEN, Chicago.

INVESTIGATIONS BY MEANS OF THE DICK TEST AND ATTEMPTS AT IMMUNIZATION AGAINST SCARLET FEVER IN THE ARMY OF FINLAND. J. WICKSTRÖM, Acta pædiat. **21**:465, 1937.

The rising incidence of scarlet fever in the army of Finland led to studies of the production of active immunity. As a preliminary study, the Dick test was made, with toxin supplied by the Behring Laboratories: Of 3,367 conscripts, 85.1 per cent reacted negatively; 2.8 per cent yielded equivocal reactions, and 12.1 per cent gave reactions that varied in intensity from 1 to 3 plus. The incidence of scarlet fever during the year following the tests was 0.34 per cent in the group composed of the negative and equivocal reactors and 20.4 per cent in the group composed of those who reacted positively. In the first series of inoculations both toxin and formaldehyde-treated anatoxin were employed. The original strength of the toxin from which the anatoxin was made was 50,000 skin test doses (STD) per cubic centimeter; as the result of the formaldehyde treatment the biologic value of the anatoxin was reduced to 1,000 STD. The author designates the potency of this material as 50,000/1,000 STD. The first dose was 5,000/100 STD; a total dose of from 85,000/1,700 to 160,000/3,200 STD was given in three injections. No untoward effects were observed. Of 57 men who gave a positive reaction in the Dick test before inoculation, 81 per cent yielded a negative reaction afterward. Seventy-four men whose reaction was positive were inoculated with unmodified toxin in initial doses of from 500 to 1,500 STD and total doses of between 35,000 and 90,000 STD. Subsequently 75.7 per cent exhibited a negative reaction. In some cases the inoculation was followed by a general reaction.

A second and larger series of conscripts was then subjected to the Dick test. Of 19,783 men, 78.8 per cent reacted negatively, 6.7 per cent equivocally and 14.5 per cent positively. The reactions of the last group varied in intensity from 1 to 3 plus. Approximately two thirds of the positively reacting conscripts were inoculated according to the previous schedule, with undenatured Dick toxin prepared, as before, from the Dochez strain of hemolytic streptococci. In the majority of cases the period of follow-up observation was one year; in some cases it was only six months. During this period the incidence of scarlet fever in the conscripts whose reaction was negative was 1.2 per cent; that in the conscripts whose reaction was positive and who had not been inoculated, 14.4 per cent; that in the positively reacting conscripts who had not received the complete course of inoculations, 23.3 per cent, and that in the positively reacting conscripts who had received the scheduled series of injections, 4 per cent. An inquiry into the cause of the failure to immunize some of the men led to the conjecture that better results might be attainable by the use of Dick toxin prepared from native or local scarlet fever streptococci.

McCUNE, New York.

Chronic Infectious Diseases

INTRACUTANEOUS TUBERCULIN REACTION ASSOCIATED WITH CALCIFIED INTRATHORACIC LESIONS. W. E. NELSON, A. G. MITCHELL and E. W. BROWN, Am. Rev. Tuberc. **37**:311 (March) 1938.

In the course of repeated cutaneous testing of a large group of children, it was found that low grade or healed tuberculous lesions may exist when the tuberculin reaction is negative or only questionably positive after intracutaneous injection of tuberculin in amounts up to 0.005 mg. of purified protein derivative and of 0.1 cc. of a 1:100 dilution of old tuberculin.

EUGENE H. SMITH, Ogden, Utah.

INTRACUTANEOUS TUBERCULIN TEST. M. PARETZKY, Am. Rev. Tuberc. **38**:81 (July) 1938.

Investigations of the influence of various factors on the outcome of the Mantoux test are reported by Paretzky. Comparison of reactions on both forearms in relation to the various dilutions of tuberculin used indicated that differences in specific cutaneous hypersensitivity in different areas are of such a degree as to be of practical significance. Five hundred double tests failed to bring out any differences in the reactive potency of freshly prepared and stock solutions of tuberculin. On the other hand, it was found that the tenacity of tuberculin, i. e., its property of adhering to syringes, is such as to be a factor of clinical significance, and the influence of this factor must be properly discounted in certain types of tuberculin test. A series of comparable tests failed to demonstrate a noticeable effect on the size of the wheal produced by the injected tuberculin on the size of the reacting cutaneous area. Alcohol left wet on the skin at the site of injection probably retards somewhat the reaction to tuberculin.

EUGENE H. SMITH, Ogden, Utah.

TUBERCULOSIS SURVEY IN CHICAGO HIGH SCHOOLS. J. B. MORAK and J. S. KRUGLICK, Am. Rev. Tuberc. **38**:106 (July) 1938.

The authors' experience in testing 26,000 Chicago high school students has led them to advise abandonment of the Pirquet test, although in 6,000 tests by this technic a higher percentage of positive reactors were found than with the Mantoux test (a single dose of 0.1 mg. of old tuberculin being used). Single tests by the intracutaneous method, however, should not be depended on to determine all positive reactors. The necessity for periodic reexamination of young persons of high school age was apparent from the fact that in a group of white children with

negative reactions, retested within a period of twelve to eighteen months 4.81 per cent showed positive reactions and in a group of Negro children with negative reactions 55.93 per cent gave positive reactions when retested. In the latter group the first test was made with a single dose of 0.1 mg. of old tuberculin. The retesting was done with two doses of purified protein derivative. A follow-up of a group of students with lesions harmless according to roentgen study and without any clinical manifestations impressed these observers with the possible seriousness of the outcome of such infections.

EUGENE H. SMITH, Ogden, Utah.

LEVINSON TEST IN TUBERCULOUS MENINGITIS. M. GLEICH, Am. Rev. Tuberc. **38**:239 (Aug.) 1938.

The value of this procedure, devised some twenty years ago, is confirmed in a further series of 30 cases, reported by Gleich in this paper. The test is done as follows: One cubic centimeter of spinal fluid is placed in each of two test tubes 8 mm. in diameter. To one tube is added 1 cc. of a 1 per cent solution of mercuric chloride and to the other 1 cc. of a 3 per cent solution of sulfosalicylic acid. The tubes are shaken, stoppered and allowed to stand for twenty-four to forty-eight hours. If the height of the precipitate in the first tube is at least twice that of the precipitate in the second tube, the result of the test is positive. Gleich states that if blood is present in the spinal fluid or if serum has been given intrathecally the test should not be done. EUGENE H. SMITH, Ogden, Utah.

PATHOGENESIS OF TUBERCULOSIS IN CHILDREN. H. S. WILLIS, Am. Rev. Tuberc. **38**:336 (Sept.) 1938.

Tuberculosis in children is characterized by (1) a relatively large amount of disease anatomically, associated with involvement of the tracheobronchial lymph nodes; (2) relatively slight symptoms, and (3) marked tendency to heal in older children and high mortality in those under 2 years of age. Two distinct types of disease are encountered among children. A rapidly progressive type is found in infants and very young children, mostly in those having intimate and extensive exposure; there is widespread involvement of the lungs and lymph nodes, often terminating in generalized tuberculosis or tuberculous meningitis. In children above this age a more or less self-healing type of disease is observed and is generally referred to as "first infection tuberculosis" or to the "childhood type." Since Willis chooses to consider the problem of childhood tuberculosis from the standpoint of dynamics rather than from that of cellular pathology, he discusses some of the factors that determine the peculiar pathologic responses in young patients. Environmental influences and frequent and intimate association with infected persons he considers of more importance than age in the tuberculosis of infancy and early childhood. Varying virulence of the strain of the infecting organism does not satisfactorily account for the differing responses to infection of children occupying the same environment. It is much more likely that the variation in numbers of bacilli, the frequency and manner of intake, and personal or individual variation in susceptibility are the determining factors. The infectious diseases of childhood, while not having the baneful influence on tuberculous infection once attributed to them, under certain circumstances appear to affect the disease unfavorably. Anatomic peculiarities in the child's lungs, especially of the lymphatic channels, may to some extent determine the prominence of the involvement of the tracheobronchial lymph nodes at this age. Summarizing his analysis of the question of the influence of previous tuberculous infection, Willis states that "until we can learn many more facts than are now known about immune phenomena, type of reaction to first and subsequent infection, the intensity of exposure, the degree and type of residual disease in those having had childhood type, we are unable to arrive dogmatically at conclusions as to protection from

first infection, though this seems highly probable, and certainly we cannot, as some have done, assume that first infection predisposes to adult type of disease. The fact that tuberculosis is prone to heal, suggests strongly the operation of resistance or immunity."

EUGENE H. SMITH, Ogden, Utah.

SYPHILIS AND GONOCOCCAL INFECTIONS IN CHILDREN. JOHN L. RICE, Arch. Pediat. **55**:583 (Oct.) 1938.

The solution of the problem of syphilis and gonococcic infections in children depends largely on three factors—education, legislation and medication. Several special legal requirements furnish a background for helpful action; the reporting of all cases of venereal disease; the requirements of drops in the eyes of the newborn and more recently, in some states, a law requiring medical examination before marriage and another requiring an antepartum examination of the blood.

ORR, Buffalo.

PUBLIC HEALTH ASPECTS OF SYPHILIS IN CHILDREN. T. ROSENTHAL, Arch. Pediat. **55**:585 (Oct.) 1938.

The incidence of syphilis in prenatal clinics is about 6 per cent in white patients and about 15 per cent in Negroes. In private practice the incidence of the disease is about 1 per cent.

According to census statistics for 1933 the incidence of stillbirths due to syphilis was 2.3 to 2.4 per 100 live births and the total number of stillbirths per 100 live births 3.7. Both estimates appear to be an understatement of the actual situation.

ORR, Buffalo.

CONGENITAL SYPHILIS—ITS DIAGNOSIS AND MANAGEMENT. T. B. GIVAN, Arch. Pediat. **55**:600 (Oct.) 1938.

In this article a summary of present methods of diagnosis and treatment of congenital syphilis is presented.

ORR, Buffalo.

MANIFESTATIONS OF CONGENITAL SYPHILIS IN BONES AND TEETH. R. M. MCLAUGHLIN, Arch. Pediat. **55**:621 (Oct.) 1938.

The subject is reviewed.

ORR, Buffalo.

NEUROSYPHILIS IN CHILDREN. LELAND E. HINSIE, Arch. Pediat. **55**:627 (Oct.) 1938.

The subject is reviewed.

ORR, Buffalo.

SOME FUNDAMENTAL INVESTIGATIONS ON RESISTANCE OF TUBERCLE BACILLI. H. J. CORPER and M. L. COHN, J. Bact. **35**:223 (March) 1938.

In studying the thermal and chemical (acetic acid) resistance of human tubercle bacilli the authors found that the type of medium on which the bacilli had been cultured was a determining factor. Those cultured on egg mediums containing broth usually showed greater resistance to heat and acetic acid than those cultured on a medium not containing broth. Likewise, bacilli cultured on whole egg medium with broth showed greater resistance than those cultured on glycerin broth agar. The age of the culture, within certain limits of from three to six weeks, appeared to exert no appreciable effect on the resistance of the bacilli. There was no apparent relation between the ability of a medium to support the growth of small numbers of tubercle bacilli and thermal lability or resistance to acetic acid. The use of various types of mediums, besides errors in technic, probably accounts for the wide variations in thermal resistance noted for tubercle bacilli in the literature. The thermal survival time of avian tubercle bacilli

exceeded that noted for human tubercle bacilli under the same conditions of culture and exposure to heat. This is a timely observation in view of the fact that more and more interest is being shown in infections with avian tubercle bacilli.

STOESSER, Minneapolis.

HINTON TEST: V. ADULT CONGENITAL SYPHILIS OTHERWISE UNDETECTED. A. W. CHEEVER, New England J. Med. **218**:630 (April 14) 1938.

In this report 6 cases are described in detail.

Hospital and private records show many such instances, illustrating the usefulness of the Hinton test of the blood in disclosing obscure congenital syphilis. In adults the Wassermann reaction is sometimes positive, but much more commonly it has by adulthood become negative. It has been shown how much oftener the condition can be detected by the Hinton test than by the Wassermann test. The question as to whether the Hinton reaction ever becomes spontaneously negative in such cases merits further study, but at present it appears that this seldom occurs.

GENGENBACH, Denver.

HINTON TEST: VI. SYPHILIS ACQUIRED IN CHILDHOOD. A. W. CHEEVER, New England J. Med. **218**:632 (April 14) 1938.

In an attempt to find out just what is meant by a positive Hinton reaction accompanied by a negative Wassermann reaction, the author made an especially painstaking study of some cases of this type at the Massachusetts General Hospital. One of the most interesting groups, though not a large one, comprised those who as children had accidently acquired syphilis. Nine cases are reported in detail.

From the point of view of treatment it is important to date the infection, because syphilis which is of recent origin needs attention when discovered in a person from 20 to 40 years old. If, however, it can be determined that the infection occurred in childhood, thus antedating the usual age of infection with acquired syphilis by from ten to twenty years, the patient needs less intensive treatment.

GENGENBACH, Denver.

TUBERCULOSIS IN EGYPTIAN CHILDREN. H. SHUKRY, M. ABAZA BEY and S. NAGGA, J. Egyptian M. A. **21**:319 (June) 1938.

Shukry discusses the clinical aspect of tuberculosis in Egyptian children. He differentiates between the preallergic phase and the phase of clinical signs. The diagnosis of the first phase depends on a history of contact with infection and a positive cutaneous reaction to tuberculin. The treatment consists primarily in separating the child from the infected person with whom he is in contact. This type occurs most frequently before the age of 3 years. The second, or reinfection phase he divides into two types; namely, (1) the lobar type and (2) the localized type, usually showing areas of subacute infiltration "fanning out" from the hilus. The diagnosis of the latter type depends, in addition, on the finding of bacilli in the sputum and on evidence obtained by roentgen study. With sufficient rest a complete cure can be accomplished, but parents are apt to neglect treatment.

Nagga discusses the roentgenologic aspects, which he summarizes as follows: 1. Primary tuberculosis, showing anything from a small circumscribed lesion to a diffuse infiltration, pneumonic in appearance. There may or may not be shadows representing the tracheobronchial lymph nodes, alone or associated with the foregoing manifestations: calcification is sometimes present, sometimes not. 2. Hilar tuberculosis. Though the lymph glands are invariably affected when the lung is attacked, they are sometimes affected alone, and Nagga differentiates two types, (*a*) lymphadenitis epituberculosa and (*b*) lymphadenitis tuberculosa. 3. Miliary tuberculosis, almost entirely confined to young children and often occurring in an apparently healthy child.

The preventive aspects are discussed by Bey. He remarks that though statistics are not available, there seems to be no doubt that tuberculosis plays an important part in the high mortality among children in Egypt. Among the causes of this are miserable housing with overcrowding, lack of sun and air and insufficient food. He advocates education of the public regarding the disease, better facilities for segregating patients with active infection and open air schools for children.

MULHERIN, Augusta, Ga.

TUBERCULOUS INFECTION IN CHILDHOOD. G. SANPAOLESI, Lattante **9**:231 (June) 1938.

This article represents a lecture given at the inauguration of the eighth annual antituberculosis campaign in Italy.

HIGGINS, Boston.

TWO ATYPICAL CASES OF TUBERCULOUS INFILTRATION OF THE LUNG. G. DAL BO ZANON, Lattante **9**:330 (Aug.) 1938.

The author reports the cases of 2 children 15 months of age with infiltration of the lungs, rales, dulness, fever and positive reactions to tuberculin. In each case, after a period of two years the signs had practically disappeared and the children seemed healthy.

HIGGINS, Boston.

SYPHILIS IN THE MOTHER. M. MONACELLI, Lattante **9**:240 (June) 1938.

This article concludes a previous one (*Lattante* **9**:207 [May] 1938).

HIGGINS, Boston.

PYELOCYSTITIS IN INFANCY. O. CIARDO, Prat. pediat. **15**:140 (Sept.) 1937.

This is a cursory review of the incidence, etiology and pathogenesis of pyelocystitis. The author adds nothing new.

DOOLEY, New York.

IMMUNITY TO TUBERCULOSIS. A. GISMONDI, Prat. pediat. **15**:163 (Oct.) 1937.

After a résumé of modern concepts of tuberculous allergy as evinced by positive cutaneous reactions, Gismondi relates the observations of Bezancon, which were presented before the Academy of Medicine of Paris in July 1937. The most significant findings in Bezancon's studies were that a certain percentage of infants born into and remaining within tuberculous families may show positive cutaneous reactions to tuberculin either tardily or not at all and that a certain percentage of infants born into tuberculous families and removed to institutional environments after more or less exposure may similarly show positive reactions tardily or not at all. Bezancon and his collaborators offered the hypothesis of a prolonged "anteallergic" period in which the infection remains latent, perhaps to be precipitated into a demonstrably allergic phase by some intercurrent ailment. Gismondi comments on the interpretation of these facts by this hypothesis and further speculates that infants born to tuberculous parents may be equipped with better defences against tuberculous infection than those born to nontuberculous parents.

DOOLEY, New York.

SOCIAL IMPORTANCE OF AN AMBULATORY ANTISYPHILITIC CLINIC IN AN INFANT'S HOSPITAL (BRESCIA, ITALY). A. PAGANI-CESA, Prat. pediat. **15**:199 (Nov.) 1937.

Within the hospital's district the number of syphilitic patients treated increased steadily from 83 in 1933 to 306 in 1936. Approximately one thousand injections of arsenic or bismuth preparations are given annually; approximately 600 Was-

sermann tests are made annually. The chief interest in this report would seem to lie in the fact that it was considered sufficiently important to be made before the Regional Pediatric Congress (Bergamo, Italy). DOOLEY, New York.

Diseases of Blood, Heart and Blood Vessels and Spleen

EPIDERMOID CYSTS OF THE SPLEEN. A. H. MONTGOMERY, E. T. MCENERY and A. A. FRANK, Ann. Surg. **108**:877 (Nov.) 1938.

The authors report 2 cases of epidermoid cyst of the spleen. One occurred in a girl aged 7 months and the other in a boy aged 6 months. The condition is apparently rare. The authors were unable to find that any cases had been reported since 1933, when Shawan collected reports of 3 cases and reported a case of his own. Custer in 1937 stated that he had found 5 cases of simple epidermoid cysts in 5,000 autopsies.

The cysts are usually large, solitary and lined with stratified pavement epithelium having prominent intercellular bridges. Cysts have been reported weighing as much as 3 Kg. and containing up to 1,500 cc. of chocolate-colored watery fluid. All clinical symptoms associated with these tumors are those of compression of the surrounding viscera.

The treatment in all cases has been splenectomy. BANTIN, Omaha.

THROMBOPENIC PURPURA AS COMPLICATION: ASSOCIATION WITH ACUTE MASTOIDITIS, LATERAL SINUS THROMBOSIS, STREPTOCOCCUS VIRIDANS BACTEREMIA AND MULTIPLE METASTATIC ABSCESSES. B. WELT and J. KASNETZ, Arch. Otolaryng. **27**:732 (June) 1938.

The authors report the case of a 7½ year old boy with acute mastoiditis, lateral sinal thrombosis, bacteremia due to Streptococcus viridans and multiple metastatic abscesses. The usual surgical procedure was employed for the mastoiditis. Thromboplastin packing was used daily because of the purpuric bleeding. Later, local heat and ultraviolet rays from an air-cooled quartz mercury vapor arc lamp were applied to stimulate granulation and epithelization. Despite the sufficient clinical evidence, the sinus was not obliterated. The metastatic abscesses were incised and evacuated. The cause of the purpura in this case is still questionable. The association of acute mastoiditis with purpura is infrequent. Repeated transfusions were the only therapy used in combating the sepsis and the purpura.

GREENWOOD, Chicago.

ARTERIOSCLEROSIS IN CHILDHOOD, WITH REPORT OF TWO CASES. H. G. GUILD, F. B. KINDELL and T. A. GIBSON, Bull. Johns Hopkins Hosp. **62**:159 (March) 1938.

Extensive arteriosclerosis in 2 girls, each 9 years old, is reported, with positive observations at autopsy to establish the diagnosis.

In the first patient there was complicating chronic pyelonephritis of marked degree; in the second, in spite of the occasional appearance of pus and colon bacilli in the urine, there was no anatomically demonstrable pyelonephritis. In spite of frequent periods of gross hematuria and the presence of arteriosclerotic nephritis, neither patient showed any marked impairment of renal function.

Abdominal symptoms, pain and melena, were prominent in both, and the abdominal lesions were directly or indirectly the precipitating cause of death: in the first case, through the development of intestinal ulceration, adhesions, obstruction and perforation; in the second, through interference with the intake of food and consequent inanition.

Cerebral symptoms were prominent in both, but more particularly in the second patient, in whom they appeared as an imminent cause of death, only barely forestalled by the abdominal complication.

Other signs and symptoms were typical of the disease as it is well recognized in the adult. In spite of the extreme hypertension and the marked cardiac hypertrophy, however, neither child at any time showed symptoms of myocardial failure.

AUTHOR'S SUMMARY.

PARTIAL ATRESIA OF THE MAIN BRANCHES OF THE PULMONARY ARTERY OCCURRING IN INFANCY AND ACCOMPANIED BY CALCIFICATION OF THE PULMONARY ARTERY AND AORTA. E. H. OPPENHEIMER, Bull. Johns Hopkins Hosp. **63:** 261 (Oct.) 1938.

A case of stricture of the right pulmonary artery and of the lower branch of the left pulmonary artery in an infant 17 months of age is reported. Only 5 cases of congenital stricture or atresia of a branch of the pulmonary artery were found recorded in the literature; in no case was the lesion bilateral.

On microscopic section the entire pulmonary artery as well as the aorta showed extensive calcification of the media. The process was most extensive in the region where the constriction of the pulmonary artery was most pronounced. No etiologic factor was found which would explain the calcification. Five other cases of arterial calcification occurring in infancy were found recorded in the literature, and 3 cases, in autopsy records of the Johns Hopkins Hospital. In none of these was there any stenosis of the arteries.

In the present case the stricture of the pulmonary artery was so severe that it put a strain on the right side of the heart similar to that put on the left side of the heart by coarctation of the aorta.

FROM THE AUTHOR'S SUMMARY.

PATHOGENESIS OF WERLHOF'S DISEASE. M. TORRIOLI and V. PUDDU, J. A. M. A. **111:**1455 (Oct. 15) 1938.

The authors discovered the presence of a thrombopenic substance in an extract of the spleens of patients with thrombocytopenic purpura. It was also present in weaker concentration in other tissues, as was determined by the toxic effect on the megakaryocytes of guinea pig bone marrow in tissue culture. Blood from the splenic vein contained the substance, but the arterial blood did not.

HEERSMA, Kalamazoo, Mich.

ACUTE HEMOLYTIC ANEMIA (LEDERER TYPE). E. H. BAXTER and M. W. EVERHART, J. Pediat. **12:**357 (March) 1938.

A 7 year old white girl became suddenly ill, with prostration, fever, abdominal pain, vomiting, splenomegaly, leukocytosis and rapidly developing anemia. Two weeks prior to the onset of this illness she had suffered from an acute infection of the upper part of the respiratory tract. Between 2 and 6 years she had had frequent attacks of urticaria associated with abdominal pain and vomiting following ingestion of food. The particular articles of diet which provoked these attacks were not ascertainable. Repeated blood transfusions were given, and later, liver extract and iron and ammonium citrates. She made a complete recovery. The authors discuss the causative factors underlying the anemia and express the belief that either infection or allergy may have been responsible for the anemia.

RAUH, Cincinnati.

IRON DEFICIENCY ANEMIA OF INFANCY. M. DIWANY, J. Egyptian M. A. **21:** 330 (June) 1938.

Observing breast-fed infants in the child welfare clinic at Fouad 1 Hospital, Diwany found a tendency toward a low hemoglobin level from the second month. The infants were born with a hemoglobin content of about 120 per cent. This value fell at the second week to 96 per cent, at the second month to 76 per cent,

at the sixth month to 68 per cent, at the twenty-fourth month to 65 per cent. There was a rise to 70 per cent by the third year. The author divides the children into two types, with subclassifications as follows: 1. Children suffering from deficient antenatal storage of iron: (*a*) babies born of anemic mothers, (*b*) babies born before term and (*c*) twin babies. 2. Children suffering from a deficient postnatal supply of iron: (*a*) children receiving an insufficient supply in the breast milk, owing to deficiency of the mother's diet, (*b*) children receiving artificial food, (*c*) children fed only with milk after the normal period of lactation. As a prophylactic measure he used iron and ammonium citrates incorporated in the diet from the second month. The dose was 1½ to 2 grains (0.09 to 0.13 Gm.) in water, given three times daily. For curative treatment he used the same compound in larger doses, 9 to 15 grains (0.58 to 0.97 Gm.) daily, and found increases varying from 3 to 30 per cent or more in one month. He lists the following causes for failure: (1) too short a period of treatment, (2) the presence of pyogenic infections or alimentary disturbances and (3) the use of iron salts of low iron solubility or of absolute chemical purity.

MULHERIN, Augusta, Ga.

A FORM OF PURPURA OCCURRING IN TROPICAL AFRICA. J. GEAR, South African M. J. **12**:632 (Sept. 10) 1938.

During the past year Gear, of Johannesburg, South Africa, has observed 7 cases in which onyalai occurred in South African natives. The salient features of this disease are: (1) sudden onset in a previously healthy young adult; (2) bleeding from the mucous membranes, usually of the nose and mouth, where on examination characteristic bullae are found, and petechial hemorrhages throughout the body; (3) suffusion and slight swelling of the eyes and face and swelling and tenderness of the parotid salivary glands; (4) normal or slightly elevated temperature; (5) prolonged bleeding time, normal coagulation time and variable capillary resistance; (6) profound thrombopenia, and (7) death in a high proportion of cases (3 of 7 in Gear's series). The cause of the disease is unknown. The response to transfusions and intramuscular injections of blood is good.

GONCE, Madison, Wis.

AURICULAR FIBRILLATION IN CHILDREN AND ADOLESCENTS. V. MIGLIORI, Méd. inf. **9**:230 (Aug.) 1938.

Two cases of auricular fibrillation are reported. One concerned a boy of 7 who had marked diphtheritic myocarditis, and the other, a girl of 14 with rheumatic heart disease involving both the mitral and the aortic valve. New methods in the treatment with digitalis, as recommended by Hanzlick and Meneghetti, are discussed.

HIGGINS, Boston.

SITUS INVERSUS VISCERUM WITH CONGENITAL MALFORMATION OF HEART. F. LO PRESTI-SEMINERIO and E. SAVATTERI, Lattante **9**:115 (March) 1938.

The case of a girl of 2 years with complete situs inversus viscerum and congenital malformation of the heart is reported. The child was cyanotic, and over the heart a soft thrill was felt; a systolic murmur replaced the first sound.

In spite of a negative Wassermann reaction of the mother, the facts that the mother had had two abortions, that the 4 other children were not in good health and that the father would not deny syphilitic infection suggested syphilis as a probable etiologic factor in this case.

HIGGINS, Boston.

PROPHYLAXIS OF HEART DISEASE IN CHILDHOOD. T. GUGLIELMINI, Prat. pediat. **16**:113 (April) 1938.

During a fifty year period (1887 to 1936) in Italy, the mortality of heart disease rose from 1,678 to 2,413 per million of population, while that of tubercu-

losis fell from 2,128 to 872 per million. The author presents a moving plea for the early recognition of heart disease and potential heart disease and for the social management of the problem through the schools and cardiac clinics. He describes American methods of attacking this problem, with particular reference to the New York Heart Association.

DOOLEY, New York.

ATTEMPTS TO TRANSMIT COOLEY'S ERYTHROBLASTIC ANEMIA TO FOWL. G. ERNANDEZ, Riv. di clin. pediat. **36**:252 (March) 1938.

The blood of a patient with Cooley's anemia was injected intravenously into 3 Livornese chickens 8 months old. Four months later the chickens, still healthy, were killed. No abnormality of the bone marrow, liver, spleen or blood was present grossly or histologically.

HIGGINS, Boston.

BLOOD VOLUME OF THE NORMAL CHILD. U. GALLERANI, Riv. di clin. pediat. **36**: 769 (Sept.) 1938.

Gallerani has determined the blood volumes of 92 children—approximately 4 boys and 4 girls for each age from 3 to 12 years. His method calls for intravenous injection of trypan red. The total volumes of blood were between 60 and 90 cc. per kilogram of body weight, the mean for boys being 80.8 and that for girls 73.6. Thus, 0.086 of the weight of a boy, and 0.081 of the weight of a girl, is blood. The mean percentage of cells was higher in boys (39.4) than in girls (37.9).

HIGGINS, Boston.

ENTEROCOCCIC ENDOCARDITIS. T. ROHLADER, Monatschr. f. Kinderh. **73**:361 (June) 1938.

The author reports a typical case of subacute bacterial endocarditis, the patient being a 14 year old girl. Culture of the blood revealed enterococci. The case is reported to show that the condition is not necessarily a purely streptococcic infection.

GERSTLEY, Chicago.

PATHOGENESIS OF COOLEY'S ANEMIA. K. CHOREMIS and G. SPILLIOPULOS, Monatschr. f. Kinderh. **74**:18 (July) 1938.

Choremis and Spilliopulos discuss parental hyperbilirubinemia in cases of Cooley's anemia and in cases of familial icterus gravis. He explains the condition as due to constitutional inferiority of the erythrocytes.

GERSTLEY, Chicago.

CARDIAC PUNCTURE IN CHILDREN. KLOTZ, Monatschr. f. Kinderh. **75**:238 (Sept.) 1938.

Evidently some German physicians have been giving transfusions of blood or injections of saline solution directly into the heart. The writer reports 2 cases and presents a photograph of the heart (obtained on autopsy) showing the hemopericardium resulting from such radical treatment.

GERSTLEY, Chicago.

FURTHER INVESTIGATIONS REGARDING THE INFLUENCE OF VITAMIN A ON THE THROMBOCYTES. E. LORENZ, Ztschr. f. Kinderh. **59**:499 (Feb. 8) 1938.

Lorenz previously reported that vitamin A causes an increase in the platelet count when the count is low and a decrease when it is high. In a recent publication Schiff and Hirschberger contended that the influence on thrombocytes is not due to vitamin A but to a T factor in sesame oil, which in Lorenz' experiments served as a vehicle for vitamin A. Further experiments by Lorenz confirmed his previous findings. Pure sesame oil caused no thrombocytosis in children and only

slight variations in the number of thrombocytes in guinea pigs. Vitamin A in olive oil had an effect similar to that observed when sesame oil served as the vehicle. Lorenz concludes that vitamin A rather than any substance contained in sesame oil influences the platelet count.

J. SIEMSEN, Chicago.

NEWEST METHOD OF TREATING CHILDREN FOR ANEMIA. M. GUTMAN, Pediatria polska **18**:121 (Feb.) 1938.

Liver is used mainly in treating for pernicious anemia. However, pernicious anemia is very rare in children. The author reviews extensively the contributions of foreign authors on pernicious anemia, particularly those of an American—Castle. In conclusion she states that the authors cited could not come to a definite opinion as to what is the best treatment for secondary anemia, whether liver, liver and iron, or iron alone. However, she thinks one cannot ignore the conclusions of investigators like "Rozenowny" that iron gives the best results. Finkelstein also advocates the use of iron in the treatment of children for anemia.

KRUPINSKI, Chicago.

Diseases of Nose, Throat and Ear

HEARING BEFORE AND AFTER RADICAL MASTOIDECTOMY: PLEA FOR AVOIDANCE OF THIS OPERATION BY EARLY ADEQUATE DRAINAGE; SUMMARY OF FIFTY-FOUR CASES WITH AUDIOGRAMS AND CLINICAL AND ROENTGEN FINDINGS. E. P. FOWLER, Arch. Otolaryng. **26**:387 (Oct.) 1937.

The author draws from his personal experience to determine what happens to a patient's hearing if a radical mastoidectomy is done, and if it is not done. The indications for radical mastoidectomy are listed, and the importance of taking an audiogram before proceeding to operate is stressed. From the data presented it is revealed that little or no improvement is found in the hearing after a radical mastoidectomy. Prevention of deafness, chronic suppuration and radical procedures is dependent on early and efficient care and treatment of primary inflammatory symptoms.

GREENWOOD, Chicago.

PNEUMOTHORAX COMPLICATING TRACHEOTOMY IN FULMINATING LARYNGOTRACHEOBRONCHITIS: REPORT OF A CASE. W. L. SIMPSON, Arch. Otolaryng. **26**:411 (Oct.) 1937.

Tracheotomy and the use of the bronchoscope are often life-saving measures in cases of laryngotracheobronchitis. Pneumothorax is a serious complication of laryngotracheobronchitis, necessitating tracheotomy and the use of the bronchoscope, but with careful attention and the use of oxygen many patients may be saved.

GREENWOOD, Chicago.

AIR CELLS OF PETROUS PORTION OF TEMPORAL BONE IN A CHILD FOUR AND A HALF YEARS OLD: A STUDY BASED ON WAX PLATE RECONSTRUCTIONS. B. J. ANSON, J. G. WILSON and J. P. GAARDSMOE, Arch. Otolaryng. **27**:588 (May) 1938.

In a 4½ year old child there was extensive pneumatization of the temporal bone. The apical air cells, which were continuous with the tympanic cavity, occupied a pericarotid position. Pneumatization of the antelabyrinthine area represents an extension of mucous membrane from the tympanic wall. As it encounters the carotid artery as an obstruction it becomes arboriform within the bony wall of the carotid canal, forming an annular collection of cells. Some of the apical cells are related to the auditory tube, but only by position, for no cells arise from the tube itself; they merely extend along the tube from their point of origin on the tympanic wall.

GREENWOOD, Chicago.

CONGENITAL ARTERIOVENOUS FISTULA OF THE MIDDLE EAR AND EXTERNAL AUDITORY CANAL. B. T. HORTON and B. E. HEMPSTEAD, Arch. Otolaryng. **27**:736 (June) 1938.

The cases of 2 women, one 43 and the other 53 years old, are reported. The first patient complained chiefly of pain in the left ear, stating that she was also conscious of a bruit in this ear which was synchronous with the heart beat. Closure of the left common carotid artery by digital pressure caused the bruit to cease. An eroded area below the tympanic membrane proved on close inspection to be the dura. The necessity of bearing in mind the possibility of an arteriovenous fistula when the patient complains of a rhythmic noise in one ear is stressed.

The second patient complained also of a noise which had been present for eighteen months in the right ear. The advent of this noise was abrupt and not associated with any preceding accident, injury or infection. A continuous bruit was readily detected through a stethoscope, located just posterior to the right ear and audible over the entire mastoid area.

GREENWOOD, Chicago.

PREOPERATIVE MANAGEMENT OF ACUTE STREPTOCOCCIC MASTOIDITIS. E. M. ATKINSON, Arch. Otolaryng. **28**:10 (July) 1938.

Atkinson presents an argument for delaying operation in cases of acute streptococcic mastoiditis until localization of the infection has occurred. Preoperative measures and indications for operations are discussed.

Of 19 patients who were operated on without delay, 8 had subsequent complications, and 3 died.

Of 14 patients who were treated expectantly, only 1 had a subsequent complication, and none died.

The period of hospitalization, too, is shortened by expectant treatment, the average length of stay in the hospital for the first group being thirty-three days and that for the second only twenty-seven.

GREENWOOD, Chicago.

NEW METHOD OF OPERATION FOR CONGENITAL ATRESIA OF THE POSTERIOR NARES. J. C. DONNELLY, Arch. Otolaryng. **28**:112 (July) 1938.

The case of a 4 year old girl is reported. The author stresses the advisability of exploring the nasopharynx and the choanae with a finger or an instrument during all operations on the nose or throat in children. The possibility of a choanal obstruction should be considered when there is chronic unilateral nasal discharge.

The use of a whole skin graft in this case obviated the problem of postoperative cicatricial stenosis.

GREENWOOD, Chicago.

CONGENITAL DERMATOID CYST AND FISTULA OF THE DORSUM OF THE NOSE: REPORT OF A CASE. E. W. HAGENS, Arch. Otolaryng. **28**:399 (Sept.) 1938.

The rare and interesting case of a white boy aged 4 years is presented. Osteomyelitis of the frontal bone was suspected but discounted on roentgen examination. The cyst was incised three times and operated on twice. The technic, which produced favorable results, is outlined.

This condition is very rare, American literature containing reports of only 3 cases.

The structure results from faulty development in the region of the sulcus supranasalis in the embryo.

GREENWOOD, Chicago.

TONSILLECTOMY UNDER INTRAVENOUS ANAESTHESIA IN CHILDREN SUFFERING FROM CHRONIC RESPIRATORY DISEASES. K. HUTCHISON, H. S. MITCHELL and H. MCHUGH, Canad. M. A. J. **39**:237 (Sept.) 1938.

Twenty-two cases are reported in which intravenous anesthesia was used. Pentothal sodium was used in the first group of cases and evipal in the later, larger group. In a few cases of the latter group morphine was used preoperatively. (Pentothal sodium is sodium ethyl-1-methylbutylthiobarbiturate. Evipal is C-C-cyclohexenylmethylbarbituric acid.)

The average dose of pentothal sodium employed amounted to 0.608 Gm., while of evipal 0.614 Gm. was employed. The average age of the patients was 8.9 years; the youngest patient was 3 years old and the oldest 16.

Intravenous anesthesia may be of value in selected cases, but the authors do not feel that it should displace the ordinary methods in use for healthy children.

MOORE, Omaha.

MASSIVE COLLAPSE OF LUNG FOLLOWING TONSILLECTOMY. RECOVERY. R. W. B. ELLIS, Proc. Roy. Soc. Med. **31**:772 (May) 1938.

A girl aged 9 years had suffered from asthma between the ages of 3 and 8 years. In December 1936 she had an attack of follicular tonsillitis and subsequently complained several times of sore throat. In April 1937 she was admitted to the hospital for tonsillectomy; on examination mucopus was found under the left middle turbinate and a skiagram showed well marked root shadows only. Tonsillectomy was performed and iodized poppyseed oil injected into the maxillary antrums. The operation was apparently uneventful, and there was no excessive bleeding. On the next day the temperature rose and the child appeared acutely ill. Movement of the right side of the chest was diminished. There was dulness on percussion. The breath sounds were almost completely absent over the right lung. These signs continued unchanged for three days, when the general condition improved. Roentgen study showed massive collapse of the right lung, with displacement of the heart and mediastinum to the right. Repeated roentgen examination a few days later showed expansion of the upper and middle lobe and still a few days later showed reexpansion of the whole of the right lung, with the heart in the normal position. The patient was discharged from the hospital well and free from any abnormal physical signs. WILLIAMSON, New Orleans.

Diseases of Lungs, Pleura and Mediastinum

BRONCHIECTASIS: A NEW CONCEPTION OF ITS ETIOLOGY WHICH MAKES PREVENTION AND RECOVERY POSSIBLE. S. H. WATSON and C. S. KIBLER, J. A. M. A. **111**:394 (July 30) 1938.

In 90 per cent of the authors' cases bronchiectasis or chronic cough verging on bronchiectasis is the result of long-standing allergic bronchitis, as demonstrated by the presence of eosinophils in the sputum, positive reactions to cutaneous tests and recovery after elimination of, or desensitization to, the offending substances.

HEERSMA, Kalamazoo, Mich.

SIGNIFICANCE AND TREATMENT OF COUGH IN CHILDREN. MUSTAFA EL-DIWANY, J. Egyptian M. A. **21**:368 (June) 1938.

This paper is a discussion of the many causes of this symptom and includes a number of prescriptions for "cough mixtures" of various sorts. No mention is made of allergic cough. The only unusual cause listed is that associated with intestinal parasites, e. g., Ascaris and Ankylostoma. MULHERIN, Augusta, Ga.

A SIMPLE METHOD OF BRONCHOGRAPHY FOR CHILDREN. N. M. JACOBY and G. KEATS, Lancet **2**:191 (July 23) 1938.

If iodized poppyseed oil 40 per cent is introduced into the pharynx of a child under general anesthesia it must enter the trachea. In 34 cases this principle has been applied to bronchographic study, the children being anesthetized with avertin with amylene hydrate and ether and the oil injected into the pharynx through the mouth with a syringe and cannula. The method has been found to be satisfactory and free from danger.

The child is given a course of postural drainage for several days before bronchographic study is attempted. The only thing to be guarded against at the time of bronchographic examination is the collection of iodized oil between the cheek and gums, but this will not happen if the point of the cannula is kept close to the posterior pharyngeal wall. The amount of iodized oil to be used varies with the size of the child, but the authors have never used less than 3 or more than 8 cc. for each side.

The child is kept in the semisitting position for about half a minute after the injection; he is then laid down on his back, his side or his face, depending on which lobe it is desired to fill. In many cases he is laid consecutively in all positions. An interval of two to three minutes must be allowed to elapse between injection of the iodized oil and the taking of roentgenograms.

The induction of general anesthesia in children who already have pulmonary lesions may appear to be contraindicated, but the authors state the belief that this objection is more theoretic than actual. On rare occasions general anesthesia is contraindicated.

LANGMANN, New York.

DISEASES OF THE CHEST. C. HOYLE, Practitioner **141**:430 (Oct.) 1938.

In 1938 Rogerson gave the results of an investigation into the psychic factors in asthma-prurigo in children. He found certain personality traits outstanding among these children, such as restlessness, excitability, overanxiety, irritability, aggressiveness and fear. These factors were not found to the same degree in an unselected group of normal children. The average intelligence of the asthmatic children was considerably above the average for nonasthmatic children. The difficulties of the asthmatic child were often found to have been produced by an overanxious and overprotective parental attitude. This was especially noticeable with only children. Such an asthmatic child may present many symptoms when he is at home and yet be apparently normal when away. The child takes advantage of the domestic overprotection and finds it hard to break away from a situation which gives so much satisfaction of his immediate needs; it provides security, which his overanxious nature demands, and also gives him the ability to dominate his environment. His parents watch over him uneasily, unwittingly thwarting the slightest attempts to discharge aggressive impulses along healthy lines, and with such restrictions the child rapidly becomes tense and irritable. Rogerson stressed the importance of psychic factors in causing actual attacks in some patients and showed in his series how valuable psychologic management can be as a treatment

There is now general agreement that thoracotomy should not be done for empyema until there is evidence that the effusion is localized and the mediastinum fixed. Repeated aspirations are therefore the first line of treatment. Utter in 1936 recorded 282 cases, the patients being children up to 13 years of age. The mortality among those treated by primary rib resection was 34 per cent, whereas among those treated by aspiration and later by intercostal drainage or secondary rib resection the mortality was 17 to 18 per cent. Penberry and Benson in 1936 reported a mortality of 10.3 per cent among 407 children; they used airtight drainage by intercostal catheter after aspirating repeatedly until frank pus had formed. Only 15 children required secondary rib resection. These figures show that empyema carries a lower mortality than ever before, especially among children.

GELSTON, San Francisco.

CAPILLARY STUDIES IN ACUTE PULMONARY ILLNESSES OF INFANTS. P. GORINI, Lattante **9**:64 (Feb.) 1938.

In 50 cases of bronchopneumonia, capillary changes of the skin were found on the same side as the pneumonic consolidation. The capillary resistance was diminished; the skin was paler; the visible capillaries in the nail beds were fewer, and were threadlike and the size of a pinpoint.

HIGGINS, Boston.

RAPID DEATH FROM FRANK PNEUMONIA. H. GRENET, P. ISAAC-GEORGES and R. MOUCHETTE, Bull. Soc. de pédiat. de Paris **35**:540 (Oct.) 1937.

A boy aged 7 years had pneumonia in the right lung. On the sixth day of illness he went into collapse and died a few hours thereafter. He had had no cardiac disease previously. Necropsy revealed myocardial degeneration.

BENJAMIN, Montreal, Canada.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CONSERVATIVE MANAGEMENT OF APPENDICEAL PERITONITIS IN CHILDREN. J. M. ADAMS and P. M. BANCROFT, J. Pediat. **12**:298 (March) 1938.

The purpose of this paper is the analysis of 110 cases of appendical peritonitis in children in which conservative methods of treatment were used and appendectomy deferred. The treatment consisted of continuous gastroduodenal siphonage, as instituted by Wangensteen, hot applications to the abdomen, parenteral administration of fluids and giving of sedatives. The indications for the use of conservative therapy are discussed. Age, duration of symptoms, temperature, pulse, leukocyte count and physical and roentgen findings are all important factors, but each case must be given individualized consideration. The interval between subsidence of the acute symptoms, with discharge from the hospital, and operation was about six weeks. The ideal time for deferred appendectomy has not been determined. Ten per cent of the patients had major exacerbations during the period of interval care. The mortality in this group of 110 children with appendical peritonitis treated conservatively was 4.5 per cent. There were no deaths in the group of 94 in whom appendectomy was deferred. In the younger group, 7 years and under, the mortality was 3 per cent.

RAUH, Cincinnati.

ENCOPRESIS IN CHILDREN. H. F. SHIRLEY, J. Pediat. **12**:367 (March) 1938.

Shirley uses Kanner's definition of encopresis: "involuntary defecation which is not directly due to organic illness." From Nov. 1, 1930, to March 11, 1937, 2,406 children under 15 years of age were seen in the psychiatric clinic of the Harriet Lane Home for Invalid Children, Baltimore, and, of these, 70 were encopretic, an incidence of 2.9 per cent. Encopresis was about one tenth as frequent as enuresis. Twenty-six of the 70 encopretic children were feebleminded. Twenty-one had intelligence quotients below 50, and 5, between 50 and 70. Ten of the encopretic children were of borderline intelligence (intelligence quotient, 70 to 80). Thirty-three had quotients of 80 or above. Among the intellectually adequate children encopresis in the great majority of cases was only one of many complaints. The associated complaints included enuresis, temper tantrums feeding difficulties and many other abnormalities of behavior. The frequency of the soiling episodes varied from an occasional incident to many per day. No cleancut classification of the etiologic factors was possible. Usually a combination of such factors as makeup, unhappy environment at home, interpersonal conflicts, lack of training, social difficulties, school difficulties and fears were found. Outstanding was the fact that many of the children came from unhappy homes. Oversolicitude and an overprotective attitude on the part of the mother were important factors. Of 25 intellectually adequate children of school age, 18 presented difficulties in schools. Among the intellectually adequate children 15 were physically healthy; 3 were constipated; 1 showed roentgen evidence of dilated rectum, and in 1 spina bifida was found by roentgen examination, but this was not associated with neurologic findings. Treatment was not directed solely toward relieving a symptom but was planned to help the child make a better adjustment in whatever sphere there seemed to be difficulty. The child rather than the encopresis should be treated, and in many cases the course of encopresis will run almost parallel to improvement in the general adjustment of the child.

RAUH, Cincinnati.

Summer Diarrhea. M. A. Gohar and A. Elian, J. Egyptian M. A. **21**:520 (Aug.) 1938.

This is a study of 50 cases in which there were clinical manifestations of summer diarrhea. The stools of all the patients were examined microscopically and carefully cultured. All cases in which examination disclosed amebic cysts and helminthic infection were excluded. In only 11 instances were organisms isolated which could be considered responsible for the diarrhea; in 3 instances cultures yielded Bacillus proteus, in 4 Bacillus pyocyaneus, in 2 Eberthella dysenteriae Flexner, in 1 Eberthella dysenteriae Sonne and in 1 Eberthella dysenteriae Shiga.

Twenty-four hour broth cultures of B. pyocyaneus were injected intrarectally into 3 guinea pigs and 3 rabbits; a similar number of guinea pigs and rabbits were fed on a diet contaminated with the same bacillus. The results were negative, though in all cases the organism was recovered from the feces.

Mulherin, Augusta, Ga.

Some Clinical Observations on a Series of Cases of Acute Gastro-Enteritis, with Special Reference to Treatment. M. J. Wilmers, Proc. Roy. Soc. Med. **31**:755 (May) 1938.

Thirty babies, all acutely ill, were studied. They were isolated in four rooms, and strict barrier nursing was employed. In considering the causes of the acute gastroenteritis the following points were especially noted:

1. History of exposure to infection
2. Number of children in the family
3. Previous feeding
4. Age
5. Seasonal incidence
6. Parenteral infection

All the infants were given continuous intravenous therapy, the technic of which is described in full in the report. As soon as the patients showed improvement they were fed orally. The types of milk tried and the method of feeding are discussed. The chief complications noted were: (1) thrombosis of one or more veins; (2) anorexia; (3) bronchopneumonia; (4) hematemesis; (5) hemorrhage per rectum; (6) jaundice; (7) purpura, and 8 scurvy (1 case).

Williamson, New Orleans.

Angiocholecystitis and the Meltzer-Lyon Test in Childhood. Catarrhal Nonicteric Angiocholitis in Childhood. U. Gallerani, Arch. ital. di pediat. **5**:481 (Dec.) 1937.

This is a comprehensive review of the literature followed by a report of the cases of 14 children on whom studies were made by duodenal aspiration. Three fractions of the duodenal secretion were examined, the first before, the second immediately after and the third up to one-half hour after the introduction of a solution of magnesium sulfate through the duodenal tube. Seven of the children were girls aged 9 to 12 years. They had pain in the right side of the hypochondrium and were found to have leukocytic and epithelial cell elements in the duodenal secretions, which were interpreted as indicating inflammation of the biliary tract. Seven slightly younger children, including 2 who were normal and 3 who had typical catarrhal jaundice, were used as controls and were found to have no such signs of inflammation of the biliary tract. The author concludes that there is a definite group of children, usually girls, who show nonicteric, catarrhal angiocolitis, the treatment of which may tend to prevent angiocholecystitis in later life.

The results of these studies were presented before the Societa Medico Chirurgica in Bologna, Italy in June 1937.

Dooley, New York.

PNEUMOCOCCIC PERITONITIS. G. GUASPARI, Arch. ital. di pediat. **6**:76 (Feb.) 1938.

This general review of pneumococcic peritonitis, with brief reports of 7 cases observed by the author, presents no facts or findings which are not included in modern textbooks of pediatrics.

DOOLEY, New York.

CASE OF EMBRYONAL UMBILICAL HERNIA. A. PAFUMI, Lattante **9**:110 (March) 1938.

The hernia was the size of a mandarin orange—i. e., 7 to 8 cm. in diameter—and covered with a thin reddish membrane, which later became yellowish gray; its contents, consisting of stomach, liver and part of the colon, were placed into the abdomen by operation under ethyl chloride anesthesia when the infant was 8 days old; the infant died fifteen hours later. Autopsy was performed.

Embryonal hernias come from abnormalities of development during the first three months of intrauterine life.

HIGGINS, Boston.

ELIMINATION OF HIPPURIC ACID AFTER ADMINISTRATION OF BENZOIC ACID AS A TEST OF LIVER FUNCTION IN CHILDHOOD. A. BOLLETTINO, Lattante **9**:319 (Aug.) 1938.

Bolletino has determined the state of hepatic function by the method of Yardumian and Rosenthal. This method depends on the ability of the liver to combine aminoacetic acid and benzoic acid to form hippuric acid. Each of 9 healthy children and 20 patients with diseases not involving the liver showed normal excretion of hippuric acid in the urine after administration of sodium benzoate. Fifteen children with probable hepatic disorders showed diminished excretion of hippuric acid; these children had pneumonia with enlargement of the liver, diphtheria, myocarditis, typhoid fever, catarrhal jaundice or meningococcic meningitis. Convalescence usually led to return of normal hepatic function.

HIGGINS, Boston.

APHTHOUS STOMATITIS OF POSPISCHILL. H. GOTTRON, Monatschr. f. Kinderh. **74**:82, 1938.

Gottron presents the report of a case and photographs of a 2 year old child with severe involvement. He discusses the various theories and offers some superficial scientific evidence to show that herpes simplex, aphthous stomatitis and aphthoid are different manifestations of herpetic infection.

GERSTLEY, Chicago.

Nervous Diseases

DIFFERENTIAL DIAGNOSIS OF BACTERIAL MENINGITIS OF AURAL AND OF NASAL ORIGIN. J. C. YASKIN, Arch. Otolaryng. **27**:444 (April) 1938.

Yaskin reports that meningitis originating as a complication of nasal or aural disease in 58 of 123 cases in a general hospital was found to be bacterial. The organisms isolated were streptococci, pneumococci and staphylococci. Stress is laid on the importance of differentiating between meningitis due to these microorganisms and conditions not due to invasion by known bacteria, such as cervical adenitis, meningismus and virus diseases, and other forms of bacterial meningitis, of which the commonest are the meningococcic and the tuberculous.

GREENWOOD, Chicago.

SULFANILAMIDE IN THE TREATMENT OF EXPERIMENTAL STREPTOCOCCIC AND PNEUMOCOCCIC MENINGITIS. J. A. KOLMER, A. M. RULE and M. L. WERNER, Arch. Otolaryng. **27**:519 (May) 1938.

Rabbits and monkeys were infected by means of intracisternal inoculation, symptoms developing approximately four hours after inoculation. Sulfanilamide was given four, eight and twenty-four hours after infection. Results from the intracisternal injections were not as favorable as those obtained from oral or subcutaneous administration of the compound. Best results were observed with a combination of oral administration and subcutaneous injection.

It is noted that activity of sulfanilamide apparently depends on the promotion of phagocytosis of streptococci which, most likely, is the result of some antiphagocytic substance.

Maximum doses of sulfanilamide administered as early as possible may be helpful in the treatment of streptococcic meningitis in human beings.

GREENWOOD, Chicago.

MENINGITIS OF OTITIC ORIGIN: REPORT OF TWO CASES. O. R. KLINE, Arch. Otolaryng. **27**:739 (June) 1938.

The results in 2 cases of meningitis occurring as a complication of mastoiditis are reported. In both cases the spinal fluid yielded a pure culture of Streptococcus haemolyticus.

In the first case meningitis developed nine days after mastoidectomy. The infection was relatively mild, the patient responding to one transfusion of convalescent blood.

In the second case meningeal symptoms were present from the onset of earache. Comoplete recovery was effected only after the use of sulfanilamide and prontosil (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate; now known as neoprontosil).

GREENWOOD, Chicago.

RECOVERY OF A PATIENT WITH TYPE III PNEUMOCOCCUS MENINGITIS OF OTITIC ORIGIN. J. GUBNER, Arch. Otolaryng. **28**:241 (Aug.) 1938.

Meningitis due to Pneumococcus type III is most frequently of otitic or sinal origin. When otitic meningitis is suspected, all possible foci in component parts of the temporal bone must be removed surgically. This procedure should be followed by chemotherapy and support to the tissues by blood transfusion.

Oral administration of sulfanilamide in adequate doses, resulting as it does in an almost even distribution of the drug through all the body fluids, has proved its value in the treatment of meningitis of this type by maintaining a concentration in the blood of from 8 to 10 mg. per hundred cubic centimeters.

GREENWOOD, Chicago.

HEMOLYTIC STREPTOCOCCUS MENINGITIS OF OTITIC ORIGIN: REPORT OF A RECOVERY. P. SACKS, Arch. Otolaryng. **28**:364 (Sept.) 1938.

Sacks stresses the importance of adopting a definite surgical attitude and of eliminating the primary focus without delay when meningitis occurs during an otitic infection.

An intracranial involvement, probably meningitis, should be considered when there is a history of headache and vomiting. The signs and symptoms of petrositis and the surgical approaches to the petrous pyramid should be known by all otologists. Suppurative labyrinthitis and petrositis play an important part in premeningitis therapy.

Sulfanilamide was used intraspinally in the reported case of a 6 year old boy, without irritating effect.

GREENWOOD, Chicago.

CLINICAL STUDIES IN RELATION TO ROENTGENOGRAPHIC AND NEUROSURGICAL PROCEDURES IN EPILEPSY. T. S. P. FITCH, A. W. PIGOTT and S. M. WEINGROW, Arch. Pediat. **55**:526 (Sept.) 1938.

A study of about 150 cases of institutionalized epilepsy, including a detailed investigation of the auras, pattern of attack, carotid sinus stimulation and neurologic and encephalographic findings, is reported.

In 64 cases there was no aura.

A number of reactions were obtained after stimulation of the carotid sinus. These consisted of congestion of the face, pallor, heat in the head, engorgement of the vessels of the forehead, dyspnea, dizziness, collapse, unconsciousness, epigastric distress, faintness, sleepiness, belching, feeling of falling, falling of the body to the right, falling of the head backward, movement of the eyes, ringing in the ears, jerking of various parts of the body, clonic attacks and reactions with resemblance to seizures. It remains to be seen whether the production of seizures by stimulation of the carotid sinus can be used as a means of freeing the patient from the discharge whenever it is desired.

Encephalographic Findings

	Number of Cases
Mild cortical atrophy	36
Moderate cortical atrophy	21
Marked cortical atrophy	20
Internal hydrocephalus	36
Marked internal hydrocephalus	1
External hydrocephalus	4
Arachnoiditis	26
Cerebral hemiatrophy	5
Cerebellar atrophy	1
Porencephaly	3
Vascular lesions	2
Tumor	2
Tuberculoma	2
Shortened ventricles	1
Small ventricles	1
Insufficient air injected	2
Normal encephalograms	6
Total	169

Most of the previous investigators of epilepsy have stated that there are few neurologic findings. These authors observed varied and numerous neurologic manifestations.

In their encephalographic method an attempt was made to modify the routine technic; first, an amount of air greater than the amount of fluid removed was injected in order to bring out greater details, and second, as much fluid as possible was drained.

ORR, Buffalo.

TREATMENT OF ACUTE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM WITH SULFANILAMIDE. J. B. NEAL, J. A. M. A. **111**:1353 (Oct. 8) 1938.

Neal reviews the mortality statistics of large series of cases of meningitis. The various virulent and bacterial types are mentioned, as well as the effect of sulfanilamide on each. The most remarkable change has been the reduction in mortality of meningitis due to Streptococcus haemolyticus from over 95 per cent to 20 per cent in 27 cases. Some reduction occurred in the incidence of meningococcic meningitis, little in that of pneumococcic meningitis and the other types. Drainage of the focus of infection is essential.

HEERSMA, Kalamazoo, Mich.

THE MOSCOW 2 STRAIN OF EQUINE ENCEPHALOMYELITIC VIRUS AS COMPARED WITH OTHER STRAINS OF EQUINE ENCEPHALITIC VIRUSES. B. F. HOWITT, J. Infect. Dis. **63**:269 (Nov.-Dec.) 1938.

The eastern and western American and the Moscow 2 varieties of the virus of equine encephalomyelitis show distinct differences in their periods of incubation, their temperature curves and their behavior in guinea pigs.

All three strains infect the horse and the same types of experimental animals. However, the rabbit is less susceptible to the western form than the guinea pig or the mouse.

The eastern American variety easily infects animals intracutaneously in high dilutions, while the others are less invasive by this route. The Russian form is most infective when given through the central nervous system and does not readily invade by other routes unless in comparatively large doses. Virus may be recovered from the blood serum and the tissues of animals infected with the American strains but not from those of animals infected with the Moscow 2 strain except it be from the central nervous system and occasionally from the salivary glands. The Moscow 2 strain may survive seven weeks in the ice box when diluted in water but not if diluted in saline solution. It also resists heating for ten minutes at 70 C. and can withstand freezing with solid carbon dioxide.

The eastern strain can withstand a higher hydrogen ion concentration than the other two, but all three are destroyed by high acidity. The filtrability and also the viability of all three strains are affected by the type of diluting fluid employed.

The Moscow 2 strain has a larger size than the other two, has not so far been cultivated in vitro or on the chorioallantoic membranes of the developing chick, does not confer immunity on young guinea pigs born of immune parents and is serologically and immunologically distinct from the American strains, as shown by complement fixation and neutralization tests and by cross inoculation of immune animals. Brain tissue also contains certain intracytoplasmic inclusions peculiar to this form.

The Moscow 2 strain may therefore be considered as a distinct variety of the group of viruses causing equine encephalomyelitis.

TOOMEY, Cleveland.

NEUTRALIZATION OF THE VIRUS OF ST. LOUIS ENCEPHALITIS BY SERUM FROM CHILDREN. M. G. SMITH and E. MOORE, J. Infect. Dis. **63**:319 (Nov.-Dec.) 1938.

Serum from children with cerebral involvement during the outbreak of encephalitis in 1937 was examined for the presence of antibodies that would neutralize the virus of St. Louis encephalitis. Thirteen of 23 patients (57 per cent) possessed such antibodies either during the disease or during convalescence. Of the remaining patients, the results were doubtful in regard to 1 and negative in regard to 9.

Protective substances were not found in serums from 4 children under 4½ years of age who had no history of encephalitis, but 1 of 8 such children between the ages of 7 and 13 years had these antibodies in the serum.

TOOMEY, Cleveland.

TUBEROUS SCLEROSIS OR EPILOIA: THREE CASES IN ONE FAMILY. S. E. JONES and G. P. U. PRIOR, M. J. Australia **1**:857 (May 14) 1938.

Three children came under the authors' observation because of epileptiform symptoms. In 2 of the children the first seizures occurred at 6 months and in the other at 4 months of age. The oldest child, aged 5 years, had normal intelligence, a butterfly adenoma sebaceum across the nose and cheeks, patches of leukoderma on the body and a "shagreen" patch over the sacrum. The second child, aged 2½

years, was an imbecile and had patches of leukoderma about the body but no adenoma sebaceum (which is said not to appear until about the fifth year). The third child, aged 5 months, also had patches of leukoderma.

GONCE, Madison, Wis.

TAY-SACHS DISEASE IN EGYPT. KAMEL YACOUB, J. Egyptian M. A. **21**:377 (June) 1938.

After a discussion of the general symptoms and physical findings associated with this interesting condition, the writer reports his observations on a family in which 5 of 8 siblings had Tay-Sachs disease. Two of them were seen by him; the others were included from the histories of the 2 patients. The parents of the children were related by blood, as were also the parents of the father. The family was Mohammedan.

MULHERIN, Augusta, Ga.

SEPTIC MENINGITIS: REPORT OF CASE. G. L. M. SCHOLEFIELD, New Zealand M. J. **37**:35 (Feb.) 1938.

The patient, a man 24 years old, was thrown from a motorcycle on March 29, 1937. He was unconscious for a few minutes and then went home. He remained away from work for one week, during which time a frontal headache developed. Physical examination and roentgenograms showed no abnormality, and he signed a release from the hospital after eight days, only to return April 13, 1937, with severe headache, pain in the neck and behind the eyes, photophobia and fever.

Examination showed a stiff neck and Kernig's sign on both sides. Lumbar puncture revealed opalescent spinal fluid. The cell count was 1,050 (mostly polymorphonuclears); the globulin test was markedly positive. No organisms were seen on smear or culture. The right mastoid was opened and appeared normal, but in the roof of the antrum an old clot was found. The dura appeared thick. it was incised, and free pus was obtained from beneath the temporal lobe. This was drained, and thereafter the patient slowly recovered, being given prontosil (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid) intramuscularly daily for eleven days and prontosil tablets (form not stated) by mouth. Cultures of the spinal fluid were negative throughout. No mention was made of culture of material from the abscess

MULHERIN, Augusta, Ga.

DIAGNOSIS OF MEDULLARY COMPRESSION. J. A. CHAVANY and F. THIÉBAUT, Gaz. d. hôp. **111**:101 (Jan. 22) 1938.

The authors give the histories of a group of cases, in all of which subsequent operation or autopsy verified the diagnosis.

The symptoms of medullary compression are most clearcut if the compression is caused by a subdural tumor. The site of compression is established by careful physical examination. The usual findings are discussed. The Queckenstedt test will show blockage of the subarachnoid spaces. The cerebrospinal fluid contains increased globulin and cellular elements. The test with iodized poppyseed oil 40 per cent should be done only if followed in a few hours by operation, as it may aggravate the signs. The evolution of symptoms is characteristic: slowly progressive.

The extradural tumor usually causes much more severe motor disturbances, while the objective sensory changes are slight. The signs are more of irritation than of inhibition. The evolution of signs is the same as with the subdural tumor. Roentgen examination is often of great value, as it will reveal changes in the vertebrae. On injection of iodized oil the upper and the lower border of compression are not clearly localized; the oil is broken into different little streams.

An intramedullary tumor is to be suspected if the course of illness is interrupted by spontaneous temporary improvements.

Transverse myelitis is characterized by sudden development of paraplegia, absence of block and absence of pain.

Exploratory laminectomy is the only certain means of establishing the cause of medullary compression.

KAJDI, Baltimore.

II. BEGINNINGS OF HUMAN PSYCHOLOGIC PERSONALITY. M. ACQUA, Méd. inf. **9**:211 (July) 1938.

This is a continuation of previous articles and deals with the development in the child of conceptions of time and space, of imagination and of ideas of death and religion.

HIGGINS, Boston.

ETIOLOGY OF SYDENHAM'S CHOREA. P. NOBÉCOURT, Méd. inf. **9**:225 (Aug.) 1938.

This is a clinical lecture on chorea, based on 100 cases observed by Nobécourt. Chorea was associated with cardiac and arthritic symptoms in 43 cases, with various infections, as scarlet fever, otitis media and pneumonia, in 7, and with syphilis in none. In the remaining 50 cases no definite etiologic factor was shown. The opinion is advanced that in the latter cases chorea was probably due to infection with a neurotrophic or neutrophilic virus.

HIGGINS, Boston.

PURULENT MENINGITIS IN CHILDREN. A. FARIOLI, Arch. ital. di. pediat. **5**:257 (June) 1937.

A statistical study of the records of cases of purulent meningitis in the Clinica Pediatrica (Bologna, Italy) is reported for the period from 1903 to 1936. The findings are tabulated simply, the incidence, seasonal frequency and age distribution of the various types of the disease being indicated. There is nothing unusual in these findings.

DOOLEY, New York.

CALCIUM CONTENT OF THE BLOOD OF CHILDREN IN THE PRESENCE OF HYPERKINETIC AND HYPOKINETIC STATES, PARTICULARLY CHOREA. R. FAGGIOLI and E. MEDDA, Arch. ital. di pediat. **5**:397 (Oct.) 1937.

Determinations of the calcium content of the serum were made on 65 children with various neuromuscular disturbances, including chorea (21 cases), tetany (11 cases), various convulsions (12 cases), poliomyelitis (7 cases), postdiphtheritic paralysis (6 cases), muscular dystrophy (5 cases), spastic paralysis (2 cases), and mongolism (1 case). There was constant hypocalcemia in the cases of tetany, a tendency toward hypercalcemia in the cases of postdiphtheritic paralysis and a more marked elevation in the cases of poliomyelitis. Only physiologic variations were present in the cases of chorea and the cases of other conditions named.

In a clinical consideration of 108 instances of chorea the author weighs the evidence, chiefly hyperexcitability and anodal inversion, for a parathyroid factor in the causation of chorea and concludes that the presence of such a factor is doubtful.

DOOLEY, New York.

MULTIPLE SCLEROSIS IN THREE BROTHERS. H. CURSCHMANN, Deutsche Ztschr. f. Nervenh. **145**:225, 1938.

In the family reported there were 4 brothers, 1 of whom died of diphtheria at the age of 15 years. The parents showed no signs of disease of the nervous system, nor was there any history of similar trouble in relatives. The first patient, aged 24, the youngest of the 3 survivors, had been taken ill five weeks before the case was described, with diplopia. Examination revealed nystagmus, intention tremor and spastic-ataxic gait. The deep reflexes were exaggerated, and the abdominal reflexes were absent. There were ankle clonus bilaterally and a Babinski sign on the left. Examination of the spinal fluid revealed nothing

abnormal except 20 white cells per cubic millimeter. The second patient, the eldest, aged 35, had become lame six years previously. The legs were numb and ataxic, so that he could scarcely walk. There was difficulty in urination. The right hand became unsteady. A few months after the onset the patient was found to have nystagmus, intention tremor and exaggerated deep reflexes. The abdominal reflexes were weak, and the Babinski and the Rossolimo signs were elicited. Examination of the spinal fluid showed pleocytosis and a positive colloidal gold curve. At the time the report was written, the patient was paraplegic, incontinent and euphoric and was confined to a chair. The third patient, the middle brother, aged 33, had become ill thirteen years before, at the age of 17. He had a "shock," with left hemiparesis, including the left side of the face. At that time no cause for the hemiplegia was found. The ratio of cells in the spinal fluid was 124/43/6; there was otherwise nothing remarkable. The patient improved rapidly. On examination at the time of the report, gross horizontal nystagmus was noted. The deep reflexes were exaggerated on both sides, and there were Babinski and Oppenheim signs bilaterally. Marked euphoria and scanning speech were present.

PUTNAM, Boston. [ARCH. NEUROL. & PSYCHIAT.]

THE TRYPTOPHAN TEST FOR TUBERCULOUS MENINGITIS. H. SONNEMANN, Monatschr. f. Kinderh. **73**:345 (June) 1938.

In 53 cases Sonnemann found the tryptophan test of little value in differentiating tuberculous meningitis from other types. She concludes that this test is not specific.

GERSTLEY, Chicago.

CATARRH AND ENCEPHALITIS. G. BESSAU, Monatschr. f. Kinderh. **74**:1, 1938.

Taking measles as an example, Bessau advances the hypothesis that the actual disease is the result of the action of a virus and that the catarrhal symptoms follow secondary invaders which grow on tissues weakened by the primary infection.

In encephalitis of measles there is no sign of primary invasion of the nervous system by a pyogenic organism, such as the meningococcus. On the other hand, there are no mucous membranes available for secondary catarrhal inflammation. The changes are in the brain tissue itself. The writer, reasoning backward, concludes that the encephalitis must be caused by an undiscovered virus.

GERSTLEY, Chicago.

CONVULSIVE ATTACKS IN NEUROPATHIC CHILDREN. O. BOSSERT, Monatschr. f. Kinderh. **74**:11, 1938.

Without any experimental evidence, Bossert describes attacks of syncope occurring in children as due to vasomotor instability. The children were members of neuropathic families, and the attacks occurred at about the time of puberty. The attacks sometimes followed mild psychic trauma.

GERSTLEY, Chicago.

IMPORTANCE OF AMMONIA IN THE SPINAL FLUID. H. H. BRUEHL, Ztschr. f. Kinderh. **59**:446 (Feb. 8) 1938.

Ammonia in the spinal fluid is a product of cerebral metabolism and is normally not present. In cases of cerebral stimulation ammonia is present. Bruehl studied the ammonia content of the spinal fluid in a large variety of cases. In cases of involvement of the brain stem, with spasticity, choreiform restlessness, athetosis and kinesia, there was no increase or a slight increase in the ammonia content of the spinal fluid, the value sometimes reaching 90 mg. per hundred cubic centimeters. In cases of involvement of the cerebrum itself, with convulsions, the value was higher (up to 445 mg. per hundred cubic centimeters). Thus, roughly speaking, the determination of the ammonia content of the spinal fluid permits localization of a lesion of the brain.

SIEMSEN, Chicago.

SPINAL MENINGITIS DUE TO MASTOIDITIS. W. LUXENBURG, Pediatria polska **18**:14 (Feb.) 1938.

Spinal meningitis due to mastoiditis is a frequent occurrence in recent years. Much has been written on it in Poland. The diagnosis of meningitis is not difficult when the mastoid is definitely inflamed or during an epidemic. However, when the two factors mentioned are absent, the recognition of this condition may be difficult. Luxenburg reports cases of spinal meningitis in which diagnosis was difficult because symptoms of meningitis were masked by complications—in one case by grip and in the other by sunstroke.

KRUPINSKI, Chicago.

Diseases of the Genitourinary Tract

TREATMENT OF THE BACTEREMIA OF POSTSCARLATINAL NEPHRITIS WITH PRONTOSIL AND PRONTYLIN. A. W. CHAPMAN, Arch. Pediat. **55**:560 (Sept.) 1938.

A case of postscarlatinal nephritis with uremia and streptococcic bacteremia successfully treated with prontosil and sulfanilamide is reported. Marked improvement occurred forty-eight hours after treatment had been started.

ORR, Buffalo.

PUBERTAS PRAECOX DUE TO DEXTROLATERAL GRANULOSA CELL TUMOR OF OVARY IN FOUR-YEAR-OLD GIRL. E. MANNHEIMER, J. Pediat. **12**:350 (March) 1938.

Mannheimer describes the case of a 4 year old girl who, in addition to advent of menstruation and appearance of secondary sexual distinguishing marks, showed increased growth in length and early ossification of the bones. The cause of this disturbance was a granulosa cell tumor of the right ovary. After removal of the tumor, menstruation ceased, and the child regained the childish features characteristic for her age. The breasts decreased somewhat.

This case is of special interest because of the studies of gonadotropic products carried on. The urine was analyzed for gonadotropic substances, with negative results. The Aschheim-Zondek test gave a negative result. A test for gonadotropic principle in the urine done on mice according to the Zondek method, showed less than 9 units per liter of urine, which is extremely insignificant. The tumor was analyzed for gonadotropic substances. One-tenth gram amounts of the gland were implanted in the femoral muscles of 4 mice. On the fourth day after implantation, horn scales were discovered in the vagina of a single mouse, i. e., the infantile mouse had reached her period of heat (estrus). Mannheimer believes that this may be evidence of the fact that the tumor in question contained an estrogen in greater or smaller quantity. Alcoholic extracts were made of the remainder of the tumor but proved to be ineffective; injection of the extracts into both uncastrated and castrated mice gave negative results.

RAUH, Cincinnati.

INCIDENCE OF PUS CELLS AND BACTERIA IN URINE OF CHILDREN. M. DIWANY, J. Egyptian M. A. **21**:352 (June) 1938.

Diwany reports an investigation undertaken to find out the incidence and number of pus cells and bacteria in certain definite quantities of urine of apparently healthy children and of children suffering from diseases other than actual pyelitis. The technic was to take 1 drop of a catheter specimen for culture and another drop for counting in a hemocytometer. An attempt was made to obtain the first specimen of urine passed in the morning or a specimen four hours after the "last micturition." Samples were obtained from 100 normal children (62 boys and 38 girls), from 55 children with gastroenteritis and from 50 children with thoracic trouble, such as pneumonia or bronchitis. The ages varied from 6 months to 4 years. The author's conclusions follow: 1. The urine of healthy children is usually sterile and free from pus cells, though pus cells up to 30 per cubic milli-

meter and bacteria up to 10 colonies per drop may be encountered. 2. Gastrointestinal derangements and thoracic diseases increase the incidence of pus cells and bacteria to the extent of actual pyuria or bacteriuria. By "pyuria" is meant 50 cells or more per cubic millimeter, and by "bacteriuria" is meant more than 10 colonies per drop of uncentrifuged urine.

MULHERIN, Augusta, Ga.

DISEASES OF THE KIDNEY. R. PLATT, Practitioner **141**:461 (Oct.) 1938.

In the treatment of renal rickets most authors have found that neither vitamin D nor ultraviolet irradiation is of much or any value. On account of the striking acidosis which occurs in cases of renal rickets and which, according to some authorities is the cause of the disturbance in calcium metabolism associated with the condition, Graham and Oakley (1938) gave patients with this disease large doses of alkali. The first patient received 20 grains (1.29 Gm.) each of magnesium oxide and sodium bicarbonate three times daily. There was a remarkable improvement in the function of the kidneys, with a fall in the urea content of the blood. A second patient was treated with a mixture of bismuth carbonate, magnesium oxide, sodium bicarbonate and sodium citrate equivalent to 12.4 Gm. of sodium bicarbonate per day. This did not produce such a striking improvement in renal function, but the general condition of both patients improved. They grew in height and gained weight, and the condition of their bones become much better. The improvement was, of course, only temporary, as the chronic nephritis which causes renal rickets is a progressive condition.

Such treatment might be dangerous if facilities were not at hand for keeping a constant watch on the chemical condition of the blood, for patients with renal insufficiency easily show either alkalosis or acidosis, their powers of keeping a normal acid-base balance being deficient. A condition resembling uremia can, in fact, be produced by alkalosis, dehydration and loss of sodium chloride even though the kidneys are normal.

GELSTON, San Francisco.

PYELITIS IN CHILDHOOD. O. CIARDO, Prat. pediat. **16**:35 (Feb.) 1938.

Ciardo continues his review of the subject (*Prat. Pediat.* **15**:140 [Sept.] 1937) with discussions of symptoms, prognosis and treatment, and presents 8 illustrative case records. This review is particularly interesting because general management and dietary treatment, alteration of the urine reaction, forcing of fluids, the administration of methenamine and vaccines are discussed fully, while the use of mandelic acid and treatment with sulfanilamide are not mentioned, nor are cystoscopic study and treatment considered.

DOOLEY, New York.

MALIGNANT TUMORS OF KIDNEY IN CHILDHOOD. R. JEMMA, Méd. inf. **9**:33 (Feb.) 1938.

Jemma has observed personally 19 children with malignant renal tumors. Most of the children were between 1 and 10 years of age, congenital renal tumors being rare. Histologically, the tumors were of the mixed type.

The three cardinal symptoms of renal malignancy, (1) abdominal enlargement, (2) hematuria and (3) pain, are not so uniform in children as in adults. The swelling of the abdomen is usually irregular, and in the differential diagnosis one must be on the lookout for Malta fever, kala-azar and malaria. The symptoms of the tumor may result from compression on the vena cava, on the ureters, on the intestines or on nerve tissue; edema of the extremities may be present; diarrhea following obstinate constipation may occur and also volvulus. Occasionally the tumor may lead to dyspnea, cyanosis and cough. Of the 19 children, only 3 showed early and only 2 late hematuria. Pain was much less frequent in the children than in adults, occurring in only 4 of the 19 cases. The renal function usually remained good throughout, although toxic nephritis occasionally led to diminution of function; the urine was generally normal in amount and contained albumin; only occasionally cells were found.

Anorexia and asthenia were more or less conspicuous, while fever was frequent but irregular. Metastases were common; therefore the diagnosis must be made early if surgical cure is to be hoped for.

HIGGINS, Boston.

INFLUENCE OF A RACHITOGENIC SALT DIET ON DEVELOPMENT OF THE TESTICLES. M. TEPPATI, Riv. di clin. pediat. **36**:685 (Aug.) 1938.

Eighty-five male white rats were given the rachitogenic diet of Sherman and Pappenheimer. When these animals showed rickets they were killed, and the weight, size and histologic aspect of the testicles were compared with those of the testicles of the normal litter mates. The rachitic rats were smaller than the controls, but the testicles of the rachitic rats were proportionally larger, although histologically no important change was noticed. The relatively greater development of the testicles in the rachitic rats was ascribed to hormonal and sympathicotropic action.

HIGGINS, Boston.

BLOOD UREA CLEARANCE OF VAN SLYKE AND AMBARD'S CONSTANT IN NORMAL AND PATHOLOGIC CONDITIONS IN CHILDREN. I. BIDDAU, Riv. di clin. pediat. **36**:805 (Sept.) 1938.

The urea clearance and Ambard's constant were determined for 68 normal children, for 10 children with cardiac disorders, for 2 with lipoid nephrosis and for 30 with acute glomerular nephritis. The author concludes that the urea clearance test of Van Slyke better demonstrates alterations in renal function than does the Ambard constant.

HIGGINS, Boston.

ORTHOSTATIC ALBUMINURIA. E. BECHER, Med. Klin. **34**:392 (March 25) 1938.

"Lordotic albuminuria" is a more accurate term than "orthostatic albuminuria." When the patient is in the upright position, lordosis interferes with the renal circulation and leads to albuminuria. Many subjects present disturbances of the vegetative nervous system, and atropine causes disappearance of the albuminuria. The urinary sediment may contain an occasional hyaline cast and/or leukocyte. The importance of a consideration of the condition lies in recognition of its benign nature and of its differentiation from the nephritides. No specific treatment is required. The loss of protein in the urine is not sufficiently great to necessitate a high protein diet.

SIEMSEN, Chicago.

NEPHROSIS IN CHILDHOOD. F. LINNEWEH, Monatschr. f. Kinderh. **74**:216, 1938.

Linneweh presents a general review of the subject of nephrosis, with the suggestion that the edema should be combated with large doses of urea or aminoacetic acid. It may be necessary to use from 50 to 70 Gm. of urea daily. Glycocoll may be used in amounts of 30 to 80 Gm.

GERSTLEY, Chicago.

Diseases of the Ductless Glands; Endocrinology

EFFECT OF TESTOSTERONE PROPIONATE ON NITROGEN, ELECTROLYTE, WATER AND ENERGY METABOLISM IN EUNUCHOIDISM. A. T. KENYON, I. SANDIFORD, A. H. BRYAN, K. KNOWLTON and F. C. KOCH, Endocrinology **23**:135 (Aug.) 1938.

The intramuscular administration of testosterone propionate to 4 eunuchoids, 1 of which was known to have disease of the pituitary gland, produced (1) increased frequency of erections and enlargement of the penis and the prostate gland; (2) a consistent decline in urinary nitrogen, reflected in the urea fraction, without evidence of change in the nitrogenous constituents of the blood and amounting to a retention of from 1.16 to 4.51 Gm. of nitrogen per day; (3) a decline in

urinary sodium, resulting in the retention of from 0.33 to 0.55 Gm. per day, usually a retention of chloride, and (4) a gain in weight due largely to the water held in association with the sodium and nitrogen.

Attention is called to the resemblances between the action of testosterone propionate on electrolyte excretion and that of certain of its chemical relatives among sex and adrenal hormones.

JACOBSEN, Buffalo.

INFLUENCE OF EPINEPHRINE UPON ANTIGEN AND ANTIBODY ACTION. L. TUFT, J. Allergy **9**:454 (July) 1938.

Experiments were performed in an attempt to determine whether or not the inclusion of epinephrine with an antigen or antibody would inhibit the immunizing action of the latter. Four series of experiments were carried out. It was concluded that epinephrine delays absorption of the immunizing agents but does not interfere with their specific immunizing action.

HOYER, Cincinnati.

ASSAY OF GONAD STIMULATING PREPARATIONS. M. C. D'AMOUR and F. E. D'AMOUR, J. Pharmacol. & Exper. Therap. **62**:263 (March) 1938.

This paper is probably too technical for abstraction, but certain conclusions are important, namely, that certain biologic tests are not satisfactory and, especially, that commercial preparations of the gonad-stimulating principles may show wide variation in activity; for instance, "Two pituitary products were negative on ten times the labelled dose."

PILCHER, Cleveland.

ADDISON'S DISEASE IN CHILDREN. F. R. B. ATKINSON, Brit. J. Child. Dis. **35**: 96 (April-June) 1938.

Addison first described the disease which is called by his name in 1849. The first recorded case in which the condition occurred in a child was published by Hutchinson in 1855. Atkinson lists 40 cases collected from the literature, 25 of the patients being boys and 15 being girls. Most of the patients were 10 years of age or older. The youngest patient was a 7 day old infant whose case was reported by Belaieff in 1886.

The view that tuberculosis of the adrenal glands is always found must be abandoned. In a few cases the adrenal glands were atrophied or one of them was absent; in a few they were normal. Pulmonary tuberculosis is not an uncommon finding, and lesions of the great sympathetic and the semilunar ganglions, as well as hypertrophy of the mesenteric glands, with or without tubercles, are frequent.

The disease in children is always fatal.

There are several reports of cases in which Addison's disease has been treated advantageously with the adrenal glands of sheep or with adrenal extract.

LANGMANN, New York.

INFANTILE MYXEDEMA. K. H. TALLERMAN, Proc. Roy. Soc. Med. **31**:763 (May) 1938.

The author reports the case of a girl 6½ years old. Her case had been presented at a previous meeting of the Royal Society of Medicine (*Proc. Roy. Soc. Med.* **29**:1436 [Sept.] 1938). Since that time the child had improved enormously.

WILLIAMSON, New Orleans.

EFFECTS OF "HORMONE" THERAPY IN DYSTROPHY OF INFANTS. M. ANTONINI, Lattante **9**:3 (Jan.) 1938.

Pluriglandular (thyroid, adrenal gland and testis) glycerin extracts were of therapeutic value in 7 of 8 hypotrophic infants.

HIGGINS, Boston.

Diseases of the Muscles, Bones, Joints and Lymph Glands

Osteomyelitis of the Frontal Bone. R. McKinney, Arch. Otolaryng. **28**:1 (July) 1938.

McKinney reports a growing recognition of the clinical importance of osteomyelitis of the frontal bone and expresses the opinion that the condition occurs much more frequently than would be judged by the number of cases reported. A diagnosis of chronic frontal sinusitis may be made when the infection is actually complicated by osteomyelitis.

A definite operative procedure other than the prompt and thorough removal of diseased bone is not described. Roentgenograms are useful guides but on occasion have been misleading, as bone which appears roentgenographically in good condition is sometimes undergoing osteomyelitic changes.

Prompt attention is stressed in order to avoid leptomeningitis, abscess of the brain or thrombophlebitis.

Greenwood, Chicago.

Clinical Study of Myotonic Dystrophy and Myotonia Congenita with Special Reference to Therapeutic Effect of Quinine. L. C. Kolb, A. M. Harvey and M. R. Whitehill, Bull. Johns Hopkins Hosp. **62**:188 (March) 1938.

Eight patients with myotonia atrophica and 9 patients with myotonia congenita were studied clinically while under treatment with quinine sulfate and various other drugs.

Quinine sulfate abolished myotonus but had no effect on muscular strength. It counteracted the effect of prostigmine in 2 of the patients with myasthenia gravis and increased the symptoms and signs of the disease.

Prostigmine increased myotonus and directly antagonized the full therapeutic effect of quinine sulfate.

Parathyroid extract, potassium chloride and adrenal cortical extract failed to reduce myotonus.

A brief review of the literature in relation to myotonic dystrophy is given, with a description of the disease. The clinical and laboratory data recorded for these patients are analyzed in relation to previous findings and views on pathogenesis.

Author's Summary.

Identical Dupuytren's Contracture in Identical Twins. H. Couch, Canad. M. A. J. **39**:225 (Sept.) 1938.

A case of identical Dupuytren contractures in identical twins is reported. In the left hand of each of these brothers Dupuytren's contracture occurred, making its appearance at the same age, reaching about the same degree of severity, involving the same finger in the same hand in the same manner and progressing at the same rate.

The explanation given is that this is due to variation in growth of palmar fascia, the potentiality for which is inherited.

Moore, Omaha.

Pancreatic Function and the Effect of Treatment with Pancreatic Extract in Cases of Pseudohypertrophic Muscular Dystrophy. G. M. Tosatti and G. Gherlinzoni, Arch. ital. di pediat. **5**:422 (Oct.) 1937.

Tosatti and Gherlinzoni studied pancreatic activity in 8 cases of pseudohypertrophic muscular dystrophy and found both exocrine and insular function practically normal. The use of pancreatic extracts for periods varying from two to six months resulted in little improvement in muscular function. The subjects were children ranging in age from 3 to 12 years. The methods of study included determinations of indicanuria, gross and microscopic examination of the feces, and determinations of stool fat fractions, of the enzymatic action of duodenal secretions, of carbohydrate tolerance and of insulin curves.

Dooley, New York.

BESNIER-BOECKSCHE DISEASE. W. BUJAK, Monatschr. f. Kinderh. **74**:200, 1938.

Bujak reports the case of an 11 year old girl. The disease started with small papular efflorescences on the scalp and with cervical adenopathy. In the following months the adenopathy became general, including even the bronchial lymph nodes and being accompanied with enlargements of the parotid gland, the spleen and the liver. In two years the findings had disappeared entirely. The course was afebrile. The Pirquet and the Wassermann reaction were negative. Histologic examination of an excised lymph node showed infiltration with epithelioid cells.

GERSTLEY, Chicago.

Miscellaneous

INFLUENCE OF THEOPHYLLINE UPON ABSORPTION OF MERCUPURIN AND SALYRGAN FROM SITE OF INTRAMUSCULAR INJECTION. A. C. DEGRAFF, R. C. BATTERMAN and R. A. LEHMAN, J. Pharmacol. & Exper. Therap. **62**:26 (Jan.) 1938.

Mercurial preparations were injected into the tibialis anterior muscles of normal adult rabbits. After definite intervals the muscles were excised in toto and examined for their mercury content. It was found that a compound of mercury with theophylline (mercupurin) was absorbed much more rapidly than one without (salyrgan); with the former absorption was practically 100 per cent in less than two hours. Authors have previously shown "the superiority of mercurials combined with theophylline in producing diuresis and in decreasing the local toxicity."

PILCHER, Cleveland.

ART OF DIAGNOSIS. J. C. GITTINGS, West Virginia M. J. **34**:497 (Nov.) 1938.

Laboratory data are not always conclusive. There is still need for physicians to acquire the art of evaluation and differentiation. Unnecessary laboratory work contributes largely to the high cost of medical care. Carelessness and haste account for most diagnostic errors. Histories must be taken with meticulous care, especially in the practice of pediatrics. Nothing should be taken for granted. One should not accept another physician's diagnosis but should investigate for oneself. Physical examinations should be complete. Key symptoms should be noted. The factors of probability should be remembered; multiple conditions may be coexistent. One must never let experience become merely a repetition of mistakes.

Gittings illustrates his points with examples from his personal experience.

SHAWKEY, Charleston, W. Va.

DISEASES OF CHILDREN. W. SHELDON, Practitioner **141**:386 (Oct.) 1938.

This article is part of a symposium on advances in diagnosis and treatment.

During the years since the great war the most notable advance in infant feeding has been the recognition that the main item of diet for the artificially fed infant, namely, cows' milk, whether given as fresh milk or in a dried or condensed form, can be tolerated in a less dilute strength than was formerly thought possible.

The apple treatment for diarrhea has been given a wide trial, but, while many have praised it, others have found little benefit from it. Results appear to depend largely on the careful selection of patients. The ideal patient for this treatment is the infant 6 months of age and over who is suffering from persistent diarrhea arising from prolonged injudicious feeding, with passage of loose green offensive stools containing undigested food.

The rationale of the apple treatment is not clearly understood. Its curative effect was at first attributed to pectin, but it has since been shown that pectin

given to a healthy child may actually increase the number of stools. It has also been ascribed to a colloidal effect fixing the intestinal toxins. Possibly the large amount of cellulose in the diet may act mechanically.

Of the recent chemotherapeutic agents, the sulfonamide group of drugs has had outstanding success.

Mandelic acid for the control of infections of the urinary tract has proved so effective that it is now an established agent, and during the last year or so the introduction of ammonium mandelate has simplified the treatment. Mandelic acid is effective only if the urine is kept sufficiently acid, which in effect means that the p_H of the urine must be maintained below 5.5

Infections of the nasal sinuses in childhood have only recently received the attention they deserve. Acute suppurative sinusitis is uncommon in children; it is with chronic infection that the pediatrician is mostly concerned.

The most important advance in the field of infectious fever within the last year or two has been the attempt to control outbreaks of measles by means of injections of globulin obtained from the human placenta. The prophylactic value of convalescent serum obtained from a donor who has recently recovered from measles is now firmly established. Treatment with such serum is the best method available for preventing this disease, but unfortunately the supply of serum is strictly limited.

Undulant fever, a disease due to infection with Brucella abortus, is being recognized with increasing frequency in England, and mention should therefore be made of the successful results which have followed treatment with fuadin, a complex antimony compound. Treatment consists of five injections on alternate days: for children an adequate dose would be 1 cc. on the first occasion, then 2 cc. and finally three injections of 3 cc. each. In the cases reported by Neumann from Malta the pyrexia disappeared at the end of ten days.

GELSTON, San Francisco.

RADIOLOGIC DIAGNOSIS. P. KERLEY, Practitioner **141**:538 (Oct.) 1938.

The cause of chronic mediastinal pleurisy in children is still obscure; undoubtedly the pleura is infected from mediastinal glands lying in immediate contact with it. Some workers hold that the lesion is tuberculous, but there are several records of its occurrence in children with negative reactions to the Mantoux test. The prognosis is good although after the pleura shrinks there is some traction on the bronchi of the middle and lower lobe. This dragging is probably responsible for the persistent and irritating cough associated with this condition, and it may be a potent factor in some cases of asthma.

There is still obscurity about the cause of collapse of the middle lobe in children. The bronchus of the middle lobe is small and weak compared with the bronchi of the upper and lower lobes, and normally it is surrounded by fairly numerous bronchial glands. Probably enlargement of these glands with pressure on the bronchus is the cause of collapse. In 2 cases observed by Kerley there was evidence of extensive healed tuberculosis in other parts of the lungs. As the lobe becomes deflated the upper and the lower lobe undergo compensatory emphysema, and eventually the middle lobe may be completely flattened out. This condition does not appear seriously to affect the health of the child, nor does it appear to cause the distressing chronic cough and catarrh associated with mediastinal pleurisy.

GELSTON, San Francisco.

STRYCHNINE THERAPY IN PEDIATRIC PRACTICE. A. FARIOLI, Arch. ital. di pediat. **5**:232 (June) 1937.

Farioli discusses his experience with the use of strychnine for various diseases, particularly diphtheria. His presentation consists of general remarks which do not lend themselves to critical appraisal.

DOOLEY, New York.

THE "AZOIC DERIVATIVE" IN PEDIATRIC THERAPY. R. F. KLEIN, Clin. pediat. **20:** 578 (Aug.) 1938.

This is a report of experience with "prontosil" (form not stated) in a small series of patients with various diseases in an infants' hospital in Milan, Italy. Neither the therapy nor its results are described in detail. The conclusions are that the drug is effective for streptococcic infections in general, for scarlet fever and erysipelas, for scarlatinal nephritis, for glomerulonephritis secondary to non-scarlatinal streptococcic angina and for some forms of cystitis, even that due to Bacillus coli; and that it is doubtfully effective for meningococcic meningitis, for staphylococcic or pneumococcic otitis, for certain cutaneous diseases, such as impetigo and infantile pemphigus, and for some general conditions with rhino-pharyngeal manifestations, such as grip.

DOOLEY, New York.

ITALIAN CONTRIBUTIONS TO PEDIATRICS DURING 1937. F. LO PRESTI-SEMINERIO, Lattante **9:**296 (July) 1938.

The Italian pediatric literature for 1937 contains 290 articles dealing with infants under 2 years of age. The author classifies them and gives a brief review of their subject matter.

HIGGINS, Boston.

PHYSIOPATHOLOGY AND THERAPY OF EXTENSIVE CUTANEOUS BURNS. A. GISMONDI, Prat. pediat. **15:**195 (Nov.) 1937.

This is a brief review with a discussion of indications and methods of treatment with tannic acid coagulation.

DOOLEY, New York.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

JOSEPH K. CALVIN, M.D., *President*

Regular Meeting, March 21, 1939

GEORGE F. MUNNS, M.D., *Secretary*

PERIODIC PARALYSIS. DR. ADRIAN D. M. KRAUS.

This disease is primarily a familial condition, though occasionally it occurs sporadically. It is characterized by recurrent attacks of flaccid paralysis of striated muscle, with loss of tendon reflexes and abolition of the electrical reactions. The disease may affect several members of one family; it may skip one generation and appear in several members of the next. The condition ordinarily is not present until the fifth year of life or later. Males are affected twice as often as females. Attacks may be frequent or may occur once or twice in a long life; they may be always mild or always severe or may vary in severity. During the attack there may be excessive thirst or hunger and a feeling of numbness or tingling in the extremities. The onset almost always takes place at night. The patient may awaken to find that he is more or less completely paralyzed, the weakness beginning as a rule in the legs, then extending to the arms and finally involving the trunk and neck.

The disease must be differentiated from epilepsy; the flaccid condition of the muscles and failure to lose consciousness are diagnostic features. The history and the observation of recurrent attacks of weakness or paralysis permit a definite diagnosis. If the family history divulges other cases, the diagnosis is strengthened; if the electrical reaction of the involved muscles is lost during an attack, the diagnosis is confirmed. Attacks become less frequent after middle life. Death is infrequent during attacks, but it has occurred. The definite pathologic changes which occur in the condition are not known.

I observed the case of a 16 month old boy. The literature is comprehensive.

EPIDERMOID CYSTS OF THE SPLEEN. DR. EUGENE T. MCENERY.

Epidermoid cysts of the spleen are apparently very rare. This probably accounts for the fact that epidermoid cysts are not mentioned in most surgical textbooks and are omitted from some classifications of cysts of the spleen.

A 7 year old girl was admitted to the Children's Memorial Hospital because of a splenic mass. Roentgen therapy had been used, but the mass remained unchanged. The reaction to tuberculin was positive. The diagnosis was splenic tumor due either to tuberculosis or to a neoplasm. Operation with splenectomy was performed. A large cystic mass intimately attached to the spleen was removed. The cyst contained 520 cc. of turbid chocolate-colored fluid. Pathologic examination showed it to be a true epidermoid cyst of the spleen.

The case is reported as a contribution to the limited knowledge of this rare and interesting pathologic condition with the hope that it may stimulate the report of additional cases.

DISCUSSION

DR. A. H. MONTGOMERY: These epidermoid cysts of the spleen are rare, as Dr. McEnery has pointed out. From a surgical standpoint there is not much to say. Splenectomy, the operation of choice, is relatively simple. There is little to

do except to remove the spleen with the cyst; because so little splenic tissue remains, it is hardly advisable to remove the tumor and leave the splenic tissue. I have been interested in these obscure abdominal tumors. In the first case which Dr. McEnery presented the mass in the left upper quadrant was definite. It moved with respiration and could be seen and palpated through the abdominal wall. It was apparently a splenic tumor, but the question arose whether it was tuberculous, neoplastic or parasitic. Dr. McEnery has pointed out the importance of avoiding contamination of the peritoneum in the case of a parasitic cyst.

In the second case the mass simulated a cystic tumor of the kidney, and its true origin was discovered only at autopsy. Among other instances of abdominal tumors in children were 2 cases of cystic lymphangioma of the great omentum. In one case the abdominal mass appeared to be about the size of a golf ball but proved to be much larger at operation. In the other case the mass was as large as a football. Both were removed by amputation of the omentum at the transverse portion of the colon. In another case a definite mass palpated in the left upper quadrant was thought at first to be a renal tumor but was finally diagnosed as a mesenteric cyst. At operation it proved to be a cystic tumor about the size of an orange in the transverse portion of the colon; it was fortunately amenable to surgical removal. Tumors in the right side of the abdomen are likely to be associated with the liver. In one case a palpable tumor mass appeared in the roentgenogram as a calcified mass resembling a small sea urchin. At operation it appeared to be situated in the round ligament; it was removed without difficulty. Histologically it was a calcified accessory lobe of the liver. More recently, in another case, a tumor could be seen and palpated in the right upper quadrant of the abdomen; it was easily movable from side to side but not up and down. At operation it proved to be a hepatoma arising from a tongue of liver tissue which passed through the mesocolon and extended into the cavity of the lesser omentum. It was removed without difficulty.

BROMIDE INTOXICATION IN A FOUR YEAR OLD CHILD. DR. LLOYD E. HARRIS.

During the past ten years bromide intoxication has been presented as a definite clinical entity with increasing frequency. The majority of the reports have come from psychiatric services or institutions, and the patients have usually been adults. In spite of the extensive use of bromides in the therapy of children the case of severe bromide intoxication here presented is not only unique at Children's Memorial Hospital but almost unique in the literature, only 1 other case of a similar condition in a child under 13 years of age being found. Attention is particularly directed to the profound psychic and neurologic changes, with complete absence of cutaneous lesions. The child responded rather promptly to withdrawal of bromides and to free administration of sodium chloride.

The case is recorded in the hope that it may serve as a warning and as an incentive to further observations.

DISCUSSION

DR. JOSEPH BRENNEMANN: As Dr. Harris has said, this case is unique in the experience of the staff of Children's Memorial Hospital and was of extraordinary interest to all of us. Within two weeks this child had become completely disoriented mentally and a complete wreck physically. When we tried to stand her on her feet she crumpled like a rag; her face was a mask. We had never seen anything like it. We mulled it over in our minds, obtained neurologic consultation and talked vaguely about tumor of the brain, cerebral degeneration and, of course, the usual alibi, encephalitis, although there was and had been no fever. But none of these diagnoses seemed remotely convincing. When Dr. Harris suggested bromide intoxication we gave him that friendly, tolerant look that one is apt to give to a resident who makes an unusual diagnostic suggestion. But he quickly produced some literature and conviced us that the case was typical of a condition frequently reported as occurring in adults. Most of us had associated bromide intoxication with a characteristic intractable eruption of the skin. When

the child was presented at our clinical-pathologic conference, Dr. Aron called attention to the remarkable set of cases that Dr. Gralka had reported, in which Dr. Aron had made the chemical determinations. One wonders why physicians have not observed more of these cases. An unusually large dose was given this child over a long time. As bromides are rather out of fashion, now that phenobarbital and allied drugs have come into play, it is improbable that there will be many cases such as the one here reported. It is interesting that in my earlier days, when bromides were used regularly in the treatment of epilepsy, some advised cutting down the ingestion of sodium chloride. According to what is now known of the therapy of bromide intoxication, that procedure ought to have helped bring the condition to the surface.

Dr. George F. Munns: Dr. Harris' paper is particularly timely and pertinent in view of the fact that a bromide preparation has recently been widely advocated for use in the treatment of pertussis. It is possible that with overdosage or with regular use of such a preparation during the length of time that pertussis usually persists a greater number of instances of bromide intoxication may be observed among children.

Book Reviews

Recipes and Menus for Allergics. By Myra May Haas, in collaboration with Dr. Nathan Schaffer. Menus by Cay Hillegas. Price, $2.50. Pp. 250, with 8 illustrations. New York: Dodd, Mead & Co., 1939.

This volume is an invaluable aid to the allergist and to the harrassed wife or mother who must provide sustenance for sensitive persons. Dr. Schaffer's preface, on the subject of allergy, is brief and is readily understandable to the average layman because of its explicitness, simplicity and direct style. The patient will have had the facts contained in the preface explained to him by his allergist, but reading and rereading it will serve to further his understanding of the subject and will remind him repeatedly of the pitfalls so easily overlooked. Cereals, farm products, spices, condiments, prepared foods, sauces, dressings and alcoholic and nonalcoholic beverages are discussed from the standpoint of the allergens present in food and drink.

The table of contents includes eight distinct parts: "Egg Allergy"; "Milk Allergy"; "Wheat Allergy"; "Egg and Milk Allergy"; "Egg and Wheat Allergy"; "Milk and Wheat Allergy"; "Egg, Milk and Wheat Allergy," and "Miscellaneous Allergies." A clever cartoon by O. Soglow precedes each part. An "avoid list" of foods in which the allergen or allergens may lurk, with suggestions for substitutions, prefaces each part. In this manner common pitfalls are repeatedly called to the reader's attention.

Menus for an entire week by Cay Hillegas are designed to provide balanced, varied and attractive meals. Obviously this is a great boon to the cook who faces the problem of feeding a patient whose allergist has ordered the elimination of many foods.

"Recipes and Menus for Allergics" solves the difficult problem of feeding the allergic person. Myra May Haas has provided recipes for various dishes, such as appetizers, breads, soups, poultry, meats, vegetables, salads, salad dressings and desserts. These recipes have been carefully tested and provide wide possibilities for substitution or elimination of ingredients should the patient's sensitivity demand such changes. The breads particularly, which always present difficulty to persons sensitive to wheat, provide sufficient variation to please any person, whether he is allergic or not. Desserts, too, have always been a problem, and a great number of good recipes are included. Many of the recipes are designed to feed an entire family, or to provide single portions if there is only one sensitive person in the household.

While many allergists have prepared recipes for various dishes, there are few who have the time to provide patients with sufficient recipes and menus to obviate the monotony of the diet that invariably follows. This cleverly composed cookbook at $2.50 is an excellent investment for both the allergist and the harrassed housekeeper, and fills a long-felt need. It will aid in keeping the allergist's patients contented.

Clinical and Experimental Investigations in Agranulocytosis, with Special Reference to the Etiology. By Preben Plum. Pp. 410, with 125 illustrations. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1937.

This monograph is an analysis of the findings in 88 personally collected cases of granulocytopenia, together with pertinent data from the literature. The material is discussed under the usual headings—clinical symptoms, diagnosis, pathology, etc. Thirty-six autopsies are recorded, and detailed case histories are given. The main purpose of the author, however, is to elucidate the etiology of the disease.

Plum concludes that aminopyrine is the chief cause of granulocytopenia and that in Denmark, at least, it is nearly the only cause. He presents a considerable

amount of new data in support of this contention. An analysis of the yearly incidence in Denmark shows a remarkably close correlation between the use of aminopyrine and the occurrence of the disease. Previous to 1922, when the drug began to be sold commercially on a large scale, only 3 unequivocal cases were reported or have been found on retrospective examination of hospital records. Of the 56 patients in the author's series observed between 1933 and 1936, 52 had indisputably taken aminopyrine. In only 1 case could the drug be definitely ruled out. The etiologic significance of this drug was conclusively demonstrated in 7 cases in which the patients recovered, by provoking an identical attack with small doses of aminopyrine. Examinations of the bone marrow were made at intervals, and the results were correlated with the blood picture. Tests with other drugs and an examination of the literature revealed only a few typical cases in which the condition definitely resulted from drugs other than aminopyrine. It is interesting that the author finds only 9 cases of the disease in children in which the criteria of Schultz are fulfilled.

In regard to treatment, the author is skeptical of the value of any form of therapy so far suggested.

In conclusion, the author has presented convincing evidence that aminopyrine is by far the most important causative agent in granulocytopenia.

Bereitschaft und Leistung. By M. Tramer. Price, bound, 5 francs. Pp. 84, with no illustrations. Basel: Benno Schwalbe & Co., 1938.

Bereitschaft, the author states, implies preparedness for thought, activity or emotion. Obviously, it would not be practical or even possible to discuss in an eighty-four page brochure all phases of the subject as they reflect themselves in daily biologic processes. The author has therefore limited himself to a psychobiologic discussion of thirty-six selected topics, which illustrate the existence of a predisposition, or readiness, of the human organism to react according to a certain pattern on the introduction of certain stimuli.

The existence of a *Bereitschaft,* a fertile soil, in the realm of physiology is well recognized. A predisposition of certain persons to certain diseases, for example, implies readiness of the living structure to respond to a pathogenic agent when the latter strikes the prepared soil. Tuberculosis, rheumatism and a host of other specific and nonspecific diseases are well known for their selection of more or less definite anatomic or functional types of persons. There is, as shown by the author, an analogous *Bereitschaft* of mental and emotional processes—a predisposition of human beings to react in certain definite patterns of behavior.

This interesting thesis is essentially theoretic, yet it offers much practical philosophy to the student of psychobiology.

Emotions and Bodily Changes. By H. Flanders Dunbar, M.D., Med.Sc.D., Ph.D. Second edition. Price, $5. Pp. 601. No tables or illustrations. New York: Columbia University Press, 1938.

This is a bibliography of the physiologic, psychologic, biologic, psychiatric and medical literature on psychosomatic interrelationships published since 1910. It is divided into three parts. The first deals with differentiation and integration of physical and emotional relationships. The basis for emotions, their relation to and influence on physiologic functions and the effect of emotional suppression are discussed. The relation of emotions to acute illness is considered, and the various methods of measurement are presented.

Part 2 summarizes the relation of emotions to the various systems, such as the nervous, muscular, endocrine, metabolic, cardiovascular and respiratory.

Part 3 includes an extensive bibliography, therapeutic considerations and concluding remarks.

While the book is primarily a bibliography, the excellent arrangement of the material emphasizes the prevailing, generally accepted points of view. It is therefore unified and coherent, interesting and valuable for reference.

Crystalline Enzymes: The Chemistry of Pepsin, Trypsin, and Bacteriophage. Columbia Biological Series, no. 12. By John H. Northrop. Price, $3. Pp. 176, with 48 illustrations. New York: Columbia University Press, 1939.

Every one acquainted with the field of digestion knows of the important contributions of Northrop. This book summarizes for the student of digestion and enzymes nearly all that is worth knowing on the isolation and chemistry of pepsin, trypsin and bacteriophage. Every investigator in this field will have occasion to use the book. The author points out that "bacteriophage has not been crystallized and may not be an enzyme, but the results of the experiments with bacteriophage are essentially similar to those obtained with the enzymes and are, therefore, included in the present volume." In the appendix are described methods for the estimation of pepsin and trypsin, with use of hemoglobin as a substrate. In my experience these methods are the best available and may be used with facility in the clinical laboratory. This book should be studied by all pediatricians interested in the chemistry of the digestion and the action of bacteriophage and viruses.

Les dystrophies dentaires de la syphilis héréditaire. By Lucien Lebourg. Pp. 164, with 73 illustrations. Price, 38 francs. Paris, France: G. Doin & Cie, 1939.

The author gives a detailed discussion of the dental dystrophies which occur most frequently as a result of congenital syphilis. He points out that these changes may occur as a result of other processes but that their presence indicates that syphilis should be ruled out before another cause is considered.

In general, he thinks it advisable, first, that antisyphilitic treatment should be given during the entire pregnancy of any woman presenting dental changes attributable to congenital syphilis or of any woman whose husband shows any such condition of the teeth, and second, that antisyphilitic treatment should be given during the entire pregnancy of any woman who has already given birth to children with dystrophic teeth. It is emphasized that a negative Wassermann reaction does not rule out syphilitic infection.

The book contains 73 illustrations showing normal dental development and the abnormal development found in cases of congenital syphilis.

Vingt etudes pratiques de médicine infantile. By R. Liége. Price, 60 francs. Pp. 210, with 28 illustrations. Paris: Gaston Doin & Cie, 1939.

These twenty studies concern the following conditions of infancy and childhood: pyloric stenosis; congenital hypertrophy of the neck of the bladder; appendicitis in the nursling; meningitis associated with congenital syphilis; diabetes in very young children; tetany; acrodynia; nephritis and nephrosis; encephalitis; hysteria, pithiatism, mythomania and similar disorders; the adiposogenital syndrome; acute osteomyelitis; prolonged febriculas; pneumococcic infections; pneumococcic peritonitis; abscess of the lung; bronchopneumonia, and acute edema of the lung. Organotherapy, opotherapy and blood transfusion are also discussed.

All these subjects are considered from the standpoint of etiology, symptoms and treatment, and illustrative cases are presented.

Die Neurosen des Kindesalters. By Prof. Dr. Franz Hamburger. Price, paper 12.80 marks, bound 14.60 marks. Pp. 297, with no illustrations. Stuttgart: Ferdinand Enke, 1939.

This volume was written by the director of a Viennese clinic. I have no means of knowing how far the content was influenced by the date of publication. As the book stands, the omissions are striking. For instance, it is startling to find no mention of Freud or any of his followers. It is almost equally astonishing to find no discussion of intelligence tests. Possibly because information from these two sources was deemed irrelevant, the author includes a list of drugs which he has found useful against neuroses. This book is worth having only if one is interested in the influence of political pressures on scientists.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 3-5, 1940.

American Committee:
Chairman: Dr. Henry F. Hemholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

British Paediatric Association

President: Dr. Hector C. Cameron, 23 Devonshire Pl., Upper Wimpole St., London, W. 1.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: New York. Time: June 10-14, 1940.

American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Netherland Plaza Hotel, Cincinnati. Time: Nov. 16-18, 1939.
Region I. Place: Waldorf-Astoria Hotel, New York. Time: June 1-3, 1939.
Region II. Meeting cancelled.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. R. R. MacGregor, 142 Wellington St., Kingston, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Thousand Islands Club, Alexandria Bay, N. Y. Time: June 16-17, 1939.

Society for Pediatric Research

President: Dr. L. Emmett Holt Jr., Johns Hopkins Hospital, Baltimore.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SECTIONAL

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.
Place: Memphis, Tenn. Time: Nov. 21-24, 1939.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Gilbert S. Osincup, 300 E. Colonial Dr., Orlando.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Charles Hall Farmer, 553 Walnut St., Macon.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. C. V. Calvin, 144 Golden Hill St., Bridgeport.
Secretary: Dr. E. T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Secretary-Treasurer: Dr. Philip C. de Verges, 312 Audubon Bldg., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. W. Myers Hunter, 306 N. Tryon St., Charlotte.
Secretary: Dr. J. R. Adams, 412 N. Church St., Charlotte.

Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

South Carolina Pediatric Society

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

Tennessee State Pediatric Society

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.

Texas Pediatric Society

President: T. A. Tumbleson, 2100 North St., Beaumont.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Fort Worth. Time: Oct. 14, 1939.

Virginia Pediatric Society

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

Bronx Pediatric Society

President: Dr. Samuel T. Levethan, 254 E. 184th St., Grand Concourse, New York.
Secretary: Dr. David Greene, 910 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Joseph K. Calvin, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Harold Nesbit, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St., N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Urban Busiek, 200 E. Pershing St., Springfield, Mo.
Secretary: Dr. Fred Speer, 2700 Parallel Ave., Kansas City, Kan.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Secretary: Dr. Harry Apfel, 988 Park Pl., Brooklyn, N. Y.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St., N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave., N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St., N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Secretary-Treasurer: Dr. Samuel E. Kohn, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Secretary-Treasurer: Dr. R. E. Nutting, 205 W. 2d St., Duluth, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Samuel Goldberg, 4546 N. Broad St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

St. Louis Pediatric Society

President: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of each month from September to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Clement Smith, 1101 Beacon St., Brookline, Mass.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: Horace H. Rackham Graduate School, Ann Arbor, Mich. Time: Nov. 11-12, 1938.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

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